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ARCHIVES of INTERNAL MEDICINE

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STREPTOMYCIN

Report of Its Clinical Effects in Forty-Four Patients Treated for Various Infections of the Respiratory Tract

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AND
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Medical Corps, Army of the United States

UP TO THIS writing, 44 cases of nontuberculous infections of the respiratory tract in which the patient was treated with streptomycin have been fully studied in Army hospitals. The number of cases is small because relatively few pleuropulmonary infections are caused by organisms which do not respond satisfactorily to the sulfonamide compounds and penicillin.

The sulfonamide compounds have a pronounced effect on bacterial pulmonary infections caused by Diplococcus pneumoniae (Pneumococcus) except type III and the hemolytic streptococci. Hemophilus influenzae, Klebsiella pneumoniae and Staphylococcus aureus infections are less strikingly influenced. One of the chief advantages of the sulfonamide compounds is that they are effective when administered orally. The common types of pulmonary infection which respond favorably to the sulfonamide compounds improve even more dramatically when penicillin is administered. The repeated and wearying injections necessary when this antibiotic is used are more than compensated for by the greater efficacy and relative freedom from untoward reactions. This objection may be overcome by the suggested twice daily injections of procaine-penicillin and penicillin-oil mixtures. Penicillin is effective when it is introduced into the thoracic cavity by direct injection or into the tracheobronchial tree by nebulization, either method making it possible to bring the drug into actual contact with the site of infection. An additional advantage of penicillin therapy is that penicillin is not inactivated by pus.

Notable among the nontuberculous infections of the respiratory tract which do not respond dramatically to the sulfonamide compounds and penicillin are those caused by H. influenzae and Hemophilus pertussis, K. pneumoniae, and Pasteurella tularensis. An even smaller category con-

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sists of the occasional infections caused by other organisms refractory to penicillin before therapy but sensitive to streptomycin.

REVIEW OF LITERATURE

The literature on the streptomycin therapy of nontuberculous infections of the respiratory tract is small. Case reports, for the most part dealing with single experiences,[1] indicated that lobar pneumonia caused by K. pneumoniae and bronchopneumonia caused by H. influenzae usually responded to streptomycin therapy, although they had not responded to penicillin or the sulfonamide compounds. Streptomycin was promptly established as the accepted drug in the treatment of pleuropulmonary tularemia.[2] The only published clinical experience with streptomycin in pertussis at this writing is that of Coffey and Levy[3]: Four children in whom pneumonia occurred during pertussis were treated with streptomycin; recovery followed this therapy. The patients were aged 7 weeks, 6 months, 3 years and 6 years, respectively. In 2 cases penicillin was administered prior to streptomycin, without clinical improvement. Streptomycin was given intramuscularly in doses of 100 to 200 mg. every three hours. Two premature twins, 7 weeks of age, with pertussis pneumonitis died after having shown an initial favorable response to streptomycin.

The report of the National Research Council[4] includes 44 cases of acute or chronic pulmonary infection due to a variety of organisms. None

1. Durant, T. M.; Sokalchuk, A. J.; Norris, C. M., and Brown, C. L.: Streptomycin Therapy in Hemophilus Influenzae Pulmonary Infections, J. A. M. A. **131**:194-196 (May 18) 1946. DeBakey, M. E., and Pulaski, E. J.: Analysis of Experience with Streptomycin in United States Army Hospitals: Preliminary Report, Surgery **20**:749-760 (Dec.) 1946. Bishop, C. A., and Rasmussen, R. F.: Klebsiella Pneumonia Treated with Streptomycin, J. A. M. A. **131**:821-822 (July 6) 1946. Learner, N., and Minnich, W. R.: Friedländer Pneumonia Treated with Streptomycin: Report of Case with Prompt Recovery, Ann. Int. Med. **25**:516-520 (Sept.) 1946. Geier, F. M.: Case of Friedländer's Bacillus Pneumonia Treated with Streptomycin, Permanente Found. M. Bull. **4**:159-163 (Nov.) 1946. Miller, B. W.; Orris, H. W., and Taus, H. H.: Friedländer's Pneumonia in Infancy, J. Pediat. **31**:521 (Nov.) 1947. Davis, J. P.; Cheek, K. M., and Harrell, G. T., Jr.: Friedländer Pneumonia with Bacteremia Successfully Treated with Streptomycin: Report of a Case, North Carolina M. J. **8**:767 (Dec.) 1947. Bulgrin, J. G.: Unusual Friedländer's Bacillus Pneumonia Associated with Septicemia, Radiology **50**:526-528 (April) 1948.

2. Foshay, L.: Treatment of Tularemia with Streptomycin, Am. J. Med. **2**:467-473 (May) 1947. Hunt, J. S.: Pleuropulmonary Tularemia: Observations on Twelve Cases Treated with Streptomycin, Ann. Int. Med. **26**:263-276 (Feb.) 1947. Pulaski, E. J., and Amspacher, W. H.: Streptomycin Therapy of Tularemia in U. S. Army Hospitals, Am. J. M. Sc. **214**:144-147 (Aug.) 1947.

3. Coffey, J. D., and Levy, H. B.: Streptomycin in the Treatment of Pertussis Pneumonia, Mississippi Doctor **25**:295 (Feb.) 1948.

4. Streptomycin in Treatment of Infections: Report of One Thousand Cases, Committee on Chemotherapeutics and Other Agents, National Research Council, J. A. M. A. **132**:4-11 (Sept. 7); 70-76 (Sept. 14) 1946.

of the patients had shown any effect of previous treatment with either the sulfonamide drugs or penicillin. In 17 cases the infection was due to Friedländer's bacilli. Streptomycin was extremely effective in those cases in which treatment was started early, but permanent benefits were few or transitory in the cases in which the disease process had been longer established. Three of 4 patients with H. influenzae infections recovered, and 1 died. Of 4 patients with gram-positive coccal infections, 3 were cured, and the fourth showed no improvement. The remaining 19 had various acute or chronic forms of infections with mixed gram-negative and gram-positive organisms, concerning which no conclusions were drawn.

Harris and co-workers[5] also had beneficial results from streptomycin therapy in 3 cases of pneumonia due to H. influenzae and K. pneumoniae.

Results of Streptomycin Therapy *

	Cases	Number in Which Results Were Good	Doubtful	Poor
Pneumonia due to:				
Klebsiella pneumoniae (Friedländer's bacillus)	6	6	—	—
Hemophilus influenzae	2	2	—	—
Pasteurella tularensis	3	3	—	—
Hemolytic streptococcus	1	1	—	—
Pneumococcus type IX	1	—	1	—
Pertussis with bronchopneumonia	2	—	2	—
Pneumonia with agranulocytosis	1	1	—	—
Primary atypical pneumonia	1	—	—	1
Asthma with chronic infection of the upper respiratory tract	3	—	—	3
Bronchitis	6	—	1	5
Bronchiectasis	6	2	1	3
Actinomycosis	1	—	—	1
Blastomycosis	1	—	1	—
Moniliasis	1	—	—	1
Sarcoidosis	7	—	—	7
Hodgkin's disease	2	—	—	2
Total	44	15	6	23

*The average intramuscular dose was 0.25 Gm., given every three hours. The average aerosol dose was 100 to 250 mg. dissolved in 1 to 2.5 cc., given four times a day.

In 3 cases of recurrent bronchopulmonary infection with a predominantly gram-negative flora the effects were less uniformly favorable. Drug fastness developing in the organisms not eradiacted is advanced as one of the causes of the poor clinical result.

It is too early to speak of the relative value of streptomycin as used in chronic septic bronchiectasis, but current experience[6] suggests that

5. Harris, H. W.; Murray, R.; Paine, T. F., and Finland, M.: Streptomycin Treatment of Pulmonary Infections: Clinical and Bacteriologic Studies of Six Cases, New England J. Med. **236**:611-622 (April 24) 1947.

6. Olsen, A. M.: Streptomycin Aerosol in Treatment of Chronic Bronchiectasis: Preliminary Report, Proc. Staff Meet., Mayo Clinic. **21**:53-54 (Feb. 6) 1946; Nebulization Therapy in Bronchiectasis, J. A. M. A. **134**:947-953 (July 12) 1947. Kane, L. W., and Foley, G. E.: Streptomycin Therapy in Fifty-Two Cases of Bacterial Infection, New England J. Med. **237**:531-540 (Oct. 9) 1947.

streptomycin-sensitive organisms can be reduced for a time, with change in the character and the volume of the sputum. Frequently the sputum becomes purulent after the drug has been withdrawn. Streptomycin is well tolerated when administered by the aerosol technic, whether used alone or in combination with penicillin. A few patients treated with streptomycin for empyema have shown varying responses, but details are meager in the few published reports.

In this communication we report the experiences which we have accumulated in treating pleuropulmonary infections with streptomycin in United States Army hospitals. The results of this therapy are listed in the table.

CLINICAL RESULTS

KLEBSIELLA PNEUMONIAE PNEUMONIA

CASE 1.—A 51 year old white man, after a partial gastric resection for ulcer, had chills, fever (100 F.) and pain in the chest on respiration. Signs of consolidation were present. In the sputum K. pneumoniae was predominant. On the second postoperative day, administration of streptomycin was started, 0.4 Gm. being injected intramuscularly every four hours. This dosage was continued for nine and one-half days. Within twenty-four hours there were marked clinical improvement, reduction of sputum and lowering of temperature, with uncomplicated recovery ensuing.

CASE 2.—A 29 year old soldier had chills and fever, his temperature rising to 104.5 F. He was treated for pneumococcic pneumonia; 50,000 units of penicillin was given every three hours, and 1 Gm. of sulfadiazine every four hours, for fourteen days, without effect. At this time the sputum was reported to contain Friedländer's bacilli. Streptomycin therapy was begun; 0.2 Gm. was injected intramuscularly every three hours for seven days. The patient responded after the first twelve hours of this therapy. His temperature subsided by lysis from 104.5 F. to normal within six days. The pneumonia resolved without any evidence of abscess formation.

CASE 3.—The patient was a 37 year old officer. Cyanosis and increasing signs of consolidation at the bases of both lungs developed over a five day period of sulfadiazine therapy, in the course of which this drug was given alone at the rate of 1 Gm. every four hours, then combined with penicillin, 30,000 units every three hours. Type C Friedländer bacilli were isolated from the sputum. The temperature rose to 101.8 F. daily. Streptomycin therapy was started on the sixth day, 0.5 Gm. being given every four hours. Within thirty-six hours the patient's temperature had become normal and marked clinical improvement had occurred. After nine days of therapy, considerable asymptomatic residual fibrosis or unresolved pneumonia remained. This cleared spontaneously in about thirty days.

CASE 4.—In a 36 year old soldier typical pneumonia involving the lower lobe of the left lung developed six days after inhalation anesthesia was induced for a surgical operation on the hand. His sputum contained type A Friedländer bacilli in great numbers. After four days of penicillin therapy, he showed clinical improvement but increasing consolidation. Streptomycin was then substituted for penicillin, 0.2 Gm. being given every three hours for ten days. There was com-

plete disappearance of thoracic pain, sputum and fever, and the temperature fell to normal within forty-eight hours. Serial roentgenograms of the lungs showed a gradual clearing of the pneumonic process over a two week period.

CASE 5.—A soldier aged 37 was admitted to the hospital with a one day history of severe shaking chills, high fever and a cough productive of bloody sputum. Physical examination showed an acutely ill, dyspneic patient with a temperature of 104.5 F. and fine moist rales in the right lung field. Roentgenograms showed an area of consolidation radiating from the right hilus. Combined sulfadiazine and penicillin therapy was started. Two days later there were signs of

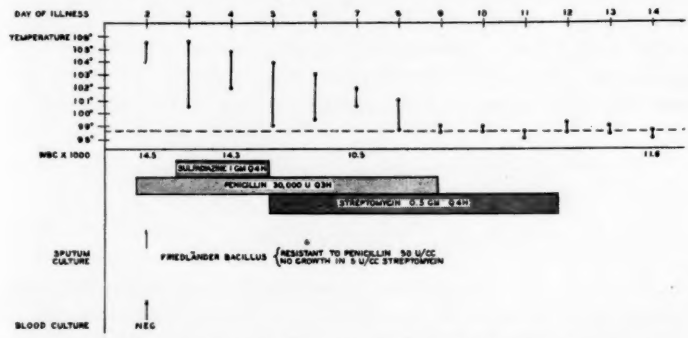

Chart 1 (case 5).—Clinical data recorded for W. M., a soldier 37 years old, who was treated with streptomycin for lobar pneumonia caused by Klebsiella pneumoniae.

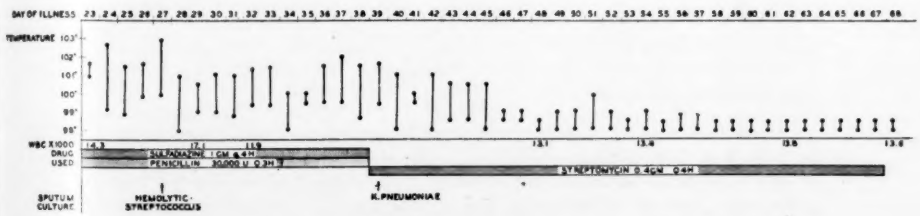

Chart 2 (case 6).—Clinical data recorded for E. M., a veteran 35 years old, who was treated with streptomycin for lobar pneumonia caused by Klebsiella pneumoniae.

consolidation over the entire right lung, shown both by physical and by roentgen examination. Culture of sputum then revealed Friedländer's bacilli. Streptomycin was immediately administered, being given in 0.25 Gm. doses every three hours together with penicillin. Within twelve hours after this therapy had been started there was a definite decrease in dyspnea and cyanosis as well as an increase in well-being. The patient's temperature subsided within seventy-two hours, and the lung fields gradually cleared.

CASE 6.—A 35 year old veteran with a five month history of cough began to have chills and fever approximately three weeks before admission. Examination revealed dulness, diminished resonance and medium loud fine rales over the

upper half of the left side of the chest. Roentgenograms showed evidence of pneumonia involving the upper lobe of the left lung with cavitation. The patient continued to have an intermittent high fever in spite of combined penicillin and sulfadiazine therapy. On the nineteenth day of hospitalization, after a report that K. pneumoniae predominated in the sputum, streptomycin therapy was started; 0.4 Gm. was given every four hours for sixteen days. The patient's temperature subsided to normal in six days and remained normal. In the ensuing month there was progressive clinical improvement. However, roentgenograms showed persisting consolidation and cavitation in the involved lobe.

In each of the foregoing 6 instances the patient remained critically ill in spite of initial empiric treatment with penicillin, alone or in combination with sulfadiazine. After sputum cultures showed Friedländer bacilli predominating, a change to streptomycin therapy was made. The response was striking in all instances, but complete clearing of the lungs varied according to the duration of the infection. Certainly, on the basis of this small experience streptomycin therapy is indicated in cases of pneumonia due to the Friedländer organisms.

HEMOPHILUS INFLUENZAE PNEUMONIA

CASE 7.—An officer aged 26 was admitted to the hospital after being ill for a week with an infection of the upper respiratory tract with chills and fever for one day. Physical examination revealed dulness and rales over the lower lobe of the right lung. His temperature was 103 F. Penicillin therapy was started, 50,000 units being administered every three hours. The dulness increased rapidly, although the temperature subsided somewhat. On the second hospital day bacilli resembling H. influenzae were seen in the sputum in great numbers, and were identified as H. influenzae subsequently. Streptomycin was substituted for penicillin, 0.4 Gm. being given every four hours. The consolidation decreased markedly after three days of this therapy and disappeared after five. By that time the patient was asymptomatic.

CASE 8.—In a 23 year old soldier with persistent atypical pneumonia of the right lung there suddenly developed a temperature of 103 F., nausea, vomiting and a pulse rate of 150. Roentgen examination showed pneumonic infiltration of the lower lobe of the left lung. The patient was given 50,000 units of penicillin every three hours and placed in an oxygen tent. After four days of therapy the entire left lung was seen to be involved. The patient was clinically unimproved. Streptomycin therapy was then started, and 0.25 Gm. was given every three hours for six days. In forty-eight hours the temperature fell to normal. The lungs were clear in nine days.

The results of the treatment of the 2 patients with pulmonary consolidation in which H. influenzae was implicated were fully as gratifying as previous reports had led us to expect.

PULMONARY TULAREMIA (3 CASES)

Three cases of pulmonary consolidation secondary to ulceroglandular tularemia have been reported previously. The patients were all young men, acutely ill, with high temperatures and general malaise, and had been shown to be infected

with P. tularensis either by rise of blood serum agglutinins or by the result of a bacteriologic examination of sputum. Streptomycin treatment was started on the seventh, twenty-first and thirty-second days of the disease, respectively, 1 to 2 Gm. being given each day. Temperatures subsided to normal within three to seven days, from levels of 104 to 105 F. The lung fields cleared in from two to four weeks.

These results, in general, confirm the published reports of the efficacy of streptomycin therapy in cases of tularemia.

COCCAL PNEUMONIA (2 CASES)

Two patients were critically ill with pneumonia due to infections which proved refractory to treatment with penicillin, though 50,000 units was administered every three hours. The first, an 18 year old white youth, was coughing up large amounts of frothy yellowish sputum containing many hemolytic streptococci. He had dulness, as well as roentgen evidence of consolidation, over the entire right lung and the upper lobe of the left lung. Streptomycin therapy was begun on the eleventh day of the disease, with 0.25 Gm. being given every three hours. This therapy resulted in gradual clearing of the chest, decrease in the volume of sputum and falling of the temperature by lysis over a period of five days. The drug was administered for ten days.

The second patient, a 17 year old soldier, had sudden sharp stabbing pain over the right lung and a temperature of 103 F. seven days after undergoing appendectomy. There was roentgenologic and clinical evidence of lobar pneumonia. The initial bacteriologic examination of the sputum suggested that K. pneumoniae was present. In view of this, streptomycin was administered at the rate of 0.5 Gm. every four hours for a total of 3 Gm. His temperature, however, showed no diminution after one and one-half days of therapy. In the meantime, Pneumococcus type IX was found in the pretreatment blood culture. Penicillin and sulfadiazine therapy in combination, substituted for streptomycin treatment, effected clearing of the pneumonia in seven days.

In the management of coccal pneumonias trial of streptomycin should be reserved for a final effort, to be made after the use of penicillin or sulfonamide drugs has failed.

PERTUSSIS WITH BRONCHOPNEUMONIA (2 CASES)

A 6 year old boy with typical clinical pertussis and bronchopneumonia but negative cough plates was given 0.25 Gm. of streptomycin every three hours for four days. The pneumonia cleared and the cough appeared decreased, but otherwise the course of the disease was not unusual.

A 4 year old girl with bronchopneumonia and pertussis had a similar course after four days of streptomycin therapy. The clinical improvement was not associated with roentgenologic evidence of clearing of the lungs.

Streptomycin may have shortened the course of the disease in these 2 children, but the actual effect of the drug is difficult to evaluate. Additional experience is necessary before any conclusions can be drawn.

OTHER PNEUMONIA (2 CASES)

In a 28 year old woman with a history of thyrotoxicosis unrelieved by two operations, severe agranulocytosis developed after two weeks' treatment with thiouracil. In spite of penicillin therapy, pneumonia developed. Her temperature reached 107 F., and her leukocyte count dropped to 800, with no granulocytes being seen. No predominating organisms were cultured. However, streptomycin was given in addition to the penicillin, and the patient survived the agranulocytic period of seven days.

In a young soldier primary atypical pneumonia developed, following bronchitis. A seven day course of parenteral streptomycin therapy was without effect.

Streptomycin apparently exerted a favorable influence in the first patient; in the second it was without effect.

DISEASES OF THE TRACHEOBRONCHIAL TREE (15 CASES)

Streptomycin was tested therapeutically in 3 cases of asthma accompanying chronic infection of the upper respiratory tract, 6 cases of chronic bronchitis and 6 cases of bronchiectasis.

Asthma with Chronic Infection of the Upper Respiratory Tract.—Streptomycin was administered by injection or by introduction of an aerosol or by a combination of the two methods. The susceptible organisms were inconstantly eliminated without clinical improvement in any of the 3 patients.

Bronchitis.—Six patients with chronic bronchitis were given streptomycin alone or combined with other therapeutic agents and by both the respiratory and the intramuscular route. The bacteriologic study showed in each case a mixed flora, with gram-negative organisms present in all cases. Gram-negative organisms were eliminated in 4 of the patients, with symptomatic relief in 1. No sustained clinical improvement occurred in 5 patients. The patient in whom clinical improvement was sustained had been treated by a combination of penicillin and streptomycin therapy.

Bronchiectasis.—Six patients with bronchiectasis were given streptomycin alone or in combination with penicillin and the streptomycin was administered by intramuscular injection or by introduction by aerosol or by both methods. All the patients had been treated previously with penicillin, administered by intramuscular injection or by introduction of an aerosol, with only slight improvement in their clinical condition. In each instance the organisms were predominantly gram-negative, and therefore streptomycin was believed to be indicated. The usual aerosol dosage was 0.1 Gm. four times daily. Two patients receiving streptomycin and penicillin were definitely improved by virtue of the elimination of susceptible bacteria, the reduction of sputum, the gain of weight and the symptomatic relief. In a third patient, receiving streptomycin alone, the sputum changed from mucopurulent to mucoid, although the quantity was not reduced. There was some subjective clinical improvement, but the actual beneficial effects of the streptomycin therapy are doubtful. In the 3 remaining patients the streptomycin had no effect in either the volume or the character of the sputum or on the patients subjectively.

Asthma related to infection of the upper respiratory tract does not seem to be favorably influenced by streptomycin therapy. Bronchitis like-

wise does not seem to be a condition favorable for this therapy, since only 1 patient in 6 showed temporary improvement. In the patients with bronchiectasis the results are equivocal; 2 patients receiving streptomycin and penicillin improved, 1 patient given streptomycin alone possibly improved, and 3 patients receiving only streptomycin were unimproved. It would seem that the best results are obtained when penicillin is given in combination with streptomycin by both the intratracheal and the intramuscular route.

OTHER DISEASES OF THE CHEST CAVITY (12 CASES)

In this category are grouped 3 cases of mycotic infection, 7 cases of pulmonary sarcoidosis and 2 cases of Hodgkin's disease.

Actinomycosis.—CASE 9.—The patient was a 20 year old man. Two weeks after he had apparently recovered from pneumonia, a fluctuant swelling developed over the left lateral and anterior wall of the chest. It was incised, and Nocardia asteroides was isolated. Despite the administration of iodides, sulfonamide compounds and massive doses of penicillin, the disease became widely disseminated, with multiple abscess formation. The fungus, which is aerobic and acid fast, was found to be sensitive to a concentration of streptomycin of 5 micrograms per cubic centimeter and resistant to penicillin. For this reason streptomycin was given, 0.5 Gm. being injected intramuscularly every four hours for twenty-four days. As a result of this treatment, several cultures of material taken from the lesion of the chest showed no growth of the fungus, and there was marked general improvement. However, severe toxic symptoms developed, chiefly nausea, vomiting, vertigo and tinnitus. Streptomycin was withdrawn. The patient again became ill, and the cultures showed growth of the fungus. A second course of streptomycin was given, lasting two weeks. Again the fungus could not be isolated from the lesions, but the general improvement was not as definite as that following the first course of therapy. Once more nausea and vomiting developed. The use of the drug had to be discontinued. A subsequent course of local application of streptomycin was ineffective. Cultures showed that the organism was now resistant to a concentration of streptomycin of 30 micrograms per cubic centimeter. "Pentamidine" (4,4' [pentamethylenedioxy] dibenzamidine) was given for about one week, but the patient died.

In this instance N. asteroides was resistant to penicillin but sensitive to streptomycin. After the patient had shown an initial good response to a course of streptomycin therapy, the fungus became resistant, and further administration of the drug was of no avail.

Blastomycosis.—CASE 10.—A 22 year old white man had chronic disease of the respiratory tract and also involvement of the chest wall. Biopsy of removed material revealed blastomycetes. The disease progressed in spite of trials of various chemotherapeutic agents. Administration of streptomycin was then begun, and 86.4 Gm. was given over a twenty-seven day period. The patient showed progressive improvement, which has been sustained during an eight month follow-up period.

The response in this patient, while not spectacular, was sufficiently gratifying to justify reporting the case at this time in view of the lack of chemotherapeutic agents effective against the disease, the outcome of which is usually fatal.

Moniliasis.—A 32 year old man was presumed to have pulmonary tuberculosis, but tubercle bacilli were not observed in his sputum, and ultimately he was found to have pulmonary moniliasis. He was given 1.8 Gm. of streptomycin a day intramuscularly in divided doses over a period of forty-two days. During the period of therapy there was a decrease of fever and cough. This improvement was attributed to suppression of secondary invaders, since the monilias were resistant to streptomycin in vitro. Serial roentgenograms showed no alteration during the use of streptomycin. Subsequent intravenous use of methylrosaniline chloride U.S.P. (gentian violet) was coincident with apparent cure.

Pulmonary Sarcoidosis.—Seven patients with pulmonary sarcoidosis were given streptomycin parenterally in amounts of 1 or 2 Gm. daily for periods of thirteen to one hundred and twelve days. No improvement followed in 6 patients. The seventh patient, during bronchoscopic examination, underwent inadvertent perforation of the wall of the esophagus. Mediastinitis resulted, with some consolidation of the base of the right lung and pleural effusion. A two week course of streptomycin therapy, 0.25 Gm. being given every four hours, resulted in clearing of the mediastinitis. The fibrosis, however, was as extensive as formerly.

Two patients with advanced mediastinal and abdominal Hodgkin's disease showed no response to streptomycin therapy.

Streptomycin therapy was of no value in the diseases of uncertain or unknown cause encountered in this series.

SUMMARY AND CONCLUSIONS

Six patients with pneumonia due to Klebsiella pneumoniae (Friedländer's bacillus) were benefited by courses of streptomycin therapy in which 0.25 to 0.4 Gm. was injected intramuscularly every three or four hours for periods of six to sixteen days. The degree of clearing of the lungs was proportionate to the duration of the infection.

Two patients with pneumonia in which Hemophilus influenzae (Pfeiffer's bacillus) was implicated responded rapidly to streptomycin.

Streptomycin is indicated for pleuropulmonary tularemia.

Patients with coccal pneumonias should be treated with streptomycin only after trial of other chemotherapeutic agents.

In 2 patients who had pertussis with bronchopneumonia no dramatic alteration of the course of the disease attended streptomycin therapy.

A patient treated with streptomycin and penicillin survived pneumonia with seven days of agranulocytosis.

Streptomycin was of no value in the treatment of 1 patient with atypical pneumonia.

One patient with blastomycosis, 1 with actinomycosis and 1 with moniliasis were treated with streptomycin. Sustained improvement and lasting remission were observed in the patient with blastomycosis. The patient who had actinomycosis showed remission only while under treat-

ment. No effect of streptomycin therapy was noted in the patient with moniliasis.

Streptomycin was of no value in the treatment of patients with chronic bronchitis.

Asthma accompanying chronic infection of the upper respiratory tract and Hodgkin's disease, pulmonary sarcoidosis and other conditions of unknown cause are not influenced by streptomycin.

ADDENDUM

Since completion of this paper 6 additional cases in which the patient was treated with streptomycin have been fully studied. They are as follows:

KLEBSIELLA PNEUMONIAE PNEUMONIA (1 CASE)

The lower lobes of the right and left lungs were involved. Streptomycin was administered for ten days after no effect was obtained with combined penicillin and sulfadiazine therapy. Twenty-four hours after the first dose of streptomycin was given, the temperature fell from 105 F. to normal levels, and there was marked clinical improvement, which was sustained and progressive.

HEMOPHILUS INFLUENZAE PNEUMONIA (1 CASE)

The lower lobes of the right and left lungs were involved. The patient, a 15 year old youth, showed marked clinical improvement within seventy-two hours after the onset of streptomycin therapy (0.25 Gm. every three hours) and steady improvement thereafter. Thirty grams of streptomycin were given over a fifteen day period.

VIRUS PNEUMONIA WITH SECONDARY PSEUDOMONAS AERUGINOSA INFECTION (1 CASE)

A 57 year old man with atypical pneumonia involving the lower lobe of the left lung suddenly became worse after twelve days of penicillin therapy. The sputum changed from blood tinged to mucopurulent. Cultures showed Ps. aeruginosa predominating, sensitive to streptomycin. He was then treated with this antibiotic, 1 Gm. being injected intramuscularly three times daily for eight days. The patient showed a slow, satisfactory response with an immediate encouraging decrease of sputum. The organisms, however, were not eliminated from the sputum and became drug fast. The patient became afebrile and symptom free on the eighth day of streptomycin therapy and remained so.

CHRONIC BRONCHITIS WITH CYLINDRIC BRONCHIECTASIS OF THE LOWER LOBE (2 CASES)

No benefit followed a two week course of combined treatment—aerosol (0.1 Gm. four times daily) and parenteral streptomycin (0.25 Gm. six times daily).

SILICOSIS (1 CASE)

A 46 year old man who had complained of cough and expectoration for six months revealed on roentgen examination splotchy, patchy infiltration throughout all lobes of both lungs, which appeared to include a moderate element of fibrosis. After one month of resting in bed there was no improvement. Streptomycin was given in a dose of 2 Gm. daily for eighty days. The condition of the patient deteriorated rapidly, and he died. At autopsy there was no gross evidence of tuberculosis. The findings were consistent with a diagnosis of severe silicosis.

BACTERIOLOGIC AND IMMUNOLOGIC STUDIES ON PATIENTS WITH HEMOLYTIC STREPTOCOCCIC INFECTIONS AS RELATED TO RHEUMATIC FEVER

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NUMEROUS investigators have studied the antibody responses of patients with either complicated or uncomplicated streptococcic infections, but only a few workers[1] have dealt with more than one or two of the antibodies to the known antigenic components of group A hemolytic streptococci. Moreover, reports which have dealt with the antibody response of patients with streptococcic complications and sequelae rarely included the period of the acute streptococcic infection in the study.

Antistreptolysin O and antifibrinolysin have been the two antibodies most commonly studied. Todd[2] originally showed that the serum antistreptolysin O titer was increased after hemolytic streptococcic infections and during the active stage of rheumatic fever. Tillett, Edwards and

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1. (*a*) McEwen, C.; Bunim, J. J., and Alexander, R. C.: Bacteriologic and Immunologic Studies in Arthritis: II. Results of Various Immunologic Tests in Different Forms of Arthritis, J. Lab. & Clin. Med. **21**:465, 1936. (*b*) Spink, W. W., and Keefer, C. S.: Studies of Hemolytic Streptococcal Infections: II. The Serological Reactions of the Blood During Erysipelas, J. Clin. Investigation **15**:21, 1936. (*c*) Mote, J. R., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: II. The Frequency of Antistreptolysin "O," Antifibrinolysin, and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections, and Rheumatic Fever, J. Immunol. **41**:61, 1941; III. The Magnitude of Anti-Streptolysin "O," Antifibrinolysin, and Precipitating-Antibody Responses; the Persistence of the Antibodies and Variations in Antistreptolysin "O" Curves in Scarlet Fever, Hemolytic Streptococcal Infections and Rheumatic Fever, ibid. **41**:87, 1941.

2. Todd, E. W.: Antihaemolysin Titres in Haemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, Brit. J. Exper. Path. **13**:248, 1932.

Garner[3] were the first to show that the plasma clot of most patients convalescent from acute hemolytic streptococcic infections became resistant to lysis by a standard culture of hemolytic streptococci, and Hadfield, Magee and Perry[4] observed that the plasma clots from patients with rheumatic fever were also resistant to lysis in the great majority of cases. These observations have been confirmed by many other workers. Antibodies in convalescent human serums against several other antigens of group A streptococci have also been studied, namely, antistreptolysin S,[5] type-specific anti-M precipitins,[6] group A specific anti-C carbohydrate precipitins,[1a] and bactericidal and bacteriostatic antibodies.[7] Type-specific agglutinins for homologous streptococci were also observed,[8] and mouse-protective antibodies were demonstrated in serums of patients recovering from group A streptococcic infections.[9]

Not only have many of these serologic studies revealed a close relationship between hemolytic streptococcic infections and rheumatic fever but they have also been applied by certain investigators to show possible differences in the antibody response between streptococci-infected patients in whom rheumatic fever developed and those in whom it did

3. Tillett, W. S.; Edwards, L. B., and Garner, R. L.: Fibrinolytic Activity of Hemolytic Streptococci: The Development of Resistance to Fibrinolysis Following Acute Hemolytic Streptococcus Infections, J. Clin. Investigation **13**:47, 1934.

4. Hadfield, G.; Magee, V., and Perry, C. B.: The Lysis of Fibrin by Streptococci: Its Application to the Problems of Rheumatic Infection in Children, Lancet **1**:834, 1934.

5. Todd, E. W.; Coburn, A. F., and Hill, A. B.: Antistreptolysin S Titres in Rheumatic Fever, Lancet **2**:1213, 1939.

6. (*a*) Swift, H. F., and Hodge, B. E.: Type Specific Anti-M Precipitins in Rheumatic and Non-Rheumatic Patients with Hemolytic Streptococcal Infections, Proc. Soc. Exper. Biol. & Med. **34**:849, 1936. (*b*) Coburn, A. F.: Observations on the Mechanism of Rheumatic Fever, Lancet **2**:1025, 1936.

7. (*a*) Todd, E. W.: The Influence of Sera Obtained from Cases of Streptococcal Septicaemia on the Virulence of the Homologous Cocci, Brit. J. Exper. Path. **8**:361, 1927. (*b*) Hare, R.: Alterations in the Bactericidal Power of the Blood Which Occur During Haemolytic Streptococcal Infections in the Puerperium, J. Path. & Bact. **41**:61, 1935. (*c*) Kuttner, A. G., and Lenert, T. F.: The Occurrence of Bacteriostatic Properties in the Blood of Patients After Recovery from Streptococcal Pharyngitis, J. Clin. Investigation **23**:151, 1944. (*d*) Rothbard, S.: Bacteriostatic Effect of Human Sera on Group A Streptococci: I. Type-Specific Antibodies in Sera of Patients Convalescent from Group A Streptococcal Pharyngitis, J. Exper. Med. **82**:93, 1945. Spink and Keefer.[1b]

8. Walker, D. W.: Application of the Technique of Slide Agglutination of Hemolytic Streptococci to Human Sera, Proc. Soc. Exper. Biol. & Med. **48**:338, 1941. Rantz, L. A.; Kirby, W. M. M., and Jacobs, A. H.: Group A Hemolytic Streptococcus Antibodies: Griffith Type Agglutinin and Antistreptolysin Titers in Normal Men and in Acute Infections, J. Clin. Investigation **22**:411, 1943.

9. Diefendorf, H. W.: A Method for Detecting in Human Serum Protective Bodies Against Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **48**:56, 1941.

not. For instance, Todd, Coburn and Hill[5] observed a contrast between the low (but increased above the normal) antistreptolysin S titer and the high antistreptolysin O titer in the serums of patients with active rheumatic fever, whereas both antistreptolysin O and antistreptolysin S titers were definitely increased in the absence of rheumatic activity after streptococcic infections. Swift and Hodge[6a] observed that anti-M precipitins appeared later in patients in whom rheumatic fever developed than in those in whom this sequela failed to appear. Coburn[6b] found that the antibody responses to streptolysin O and the type-specific M protein were delayed in rheumatic patients in whom recurrent attacks of rheumatic fever developed as compared with those who escaped recurrences after hemolytic streptococcic pharyngitis. Kuttner and Krumwiede,[10] on the other hand, have not been able to find a delayed antibody response to streptolysin O in patients in whom rheumatic fever developed after hemolytic streptococcic infections.

It is now generally believed that rheumatic fever is usually, if not invariably, preceded by infections with group A hemolytic streptococci. The mechanism by which the streptococcic infection activates rheumatic fever is still unknown. If by means of antibody studies it could be shown that rheumatic fever following streptococcic infections is characterized by a different antibody pattern than that which occurs in comparable subjects in whom rheumatic fever does not develop, then further insight might be gained concerning the mechanism by which streptococcic infections activate this disease. It appeared advisable, therefore, to extend this type of investigation for the following reasons: Many previous immunologic studies began with the period of rheumatic fever and neglected the acute streptococcic phase. Most previous investigators employed only one or two antibody reactions to hemolytic streptococcic antigens. There is still disagreement as to whether the antibody response of the rheumatic patient differs appreciably from that of the nonrheumatic patient.

All patients were followed from the time of onset of the acute streptococcic infection through the period of complications and sequelae until convalescence was well established. Serums obtained at weekly intervals were tested for the following responses:

1. Reactions induced by group A streptococci without regard to type, which included (*a*) antistreptolysin O, (*b*) antifibrinolysin, (*c*) precipitins against group A specific carbohydrate C and (*d*) precipitins against a nucleoprotein fraction obtained from group A streptococci.

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10. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three Year Study, J. Clin. Investigation **20**:273, 1941.

2. Reactions to type-specific components of group A streptococci, which included (*a*) type-specific anti-M precipitins and (*b*) type-specific bacteriostatic antibodies.

3. Reactions having no demonstrable specific relationship to streptococcic infections, which included (*a*) precipitins against pneumococcic "C" polysaccharide and (*b*) phase precipitin reactions (in 9 patients in whom rheumatic fever developed).

MATERIALS AND METHODS

Clinical Study.—From October 1940 to June 1944 a series of rheumatic and nonrheumatic subjects suffering from definite group A streptococcic nasopharyngitis was observed. They were invariably hospitalized early in the course of the primary streptococcic disease. To prevent cross infections with other types of streptococci, each patient was isolated until two successive cultures of the throat and nasopharynx, taken at least twenty-four hours apart, revealed no hemolytic streptococci. On their admission to the hospital, a complete history was recorded and a physical examination made; daily changes in signs and symptoms were uniformly documented. Routine total erythrocyte, leukocyte and differential counts, estimations of hemoglobin content, and erythrocyte sedimentation rate (Westergren), cultures of material from the nasopharynx and throat, examination of urine, electrocardiographic studies, and roentgenologic studies of the heart and lungs and the paranasal sinuses when indicated, were done at the time of entry to the hospital. Blood samples for serologic studies were obtained on admission, and at weekly intervals thereafter. In addition, serial weekly total leukocyte counts, examination of urine, electrocardiographic studies, determinations of erythrocyte sedimentation rates and cultures of material from the nasopharynx and throat (until two successive cultures taken twenty-four hours apart were sterile for hemolytic streptococci) were done.

Only symptomatic therapy was employed during the acute streptococcic phase of the illness, but patients with purulent complications were treated with sulfadiazine; many of them were also given therapeutic doses of sulfadiazine in an effort to clear up the streptococcic carrier state. All patients with rheumatic fever received adequate doses of salicylates to eliminate symptoms and fever, and this was continued throughout the period of rheumatic activity. For 1 patient it was necessary to use "pyramidon" (aminopyrine).

After discharge from the hospital, many of the rheumatic subjects were examined in the outpatient department at intervals of three to four weeks; if subsequent infections occurred, they were immediately readmitted for study.

Bacteriologic Methods.—Cultures of the nasopharynxes were obtained by passing a sterile swab through each nostril to the posterior pharyngeal wall; throat cultures were made by swabbing both tonsils or tonsillar fossae and the posterior pharynx. The swabs were streaked immediately in duplicate on fresh 5 per cent rabbit and sheep blood agar plates. Typical representative colonies were then picked and streaked on other blood agar plates for further identification or transferred directly to broth for classification. The hemolytic streptococci were grouped and typed by the precipitin technic.[11]

11. Lancefield, R. C.: The Antigenic Complex of Streptococcus Haemolyticus: I. Demonstration of a Type-Specific Substance in Extracts of Streptococcus Haemolyticus, J. Exper. Med. **47**:91, 1928. Swift, H. F.; Wilson, A. T., and Lancefield, R. C.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**:127, 1943.

Serologic Technics.—Determinations of antistreptolysin O titers were made according to Todd's method[12] modified as previously described.[13] The antifibrinolysin tests were performed by the method of Tillet, Edwards and Garner[3] and that of Boisvert.[14]

For the various precipitin tests, the following reagents were employed. The group A specific carbohydrate C was made by Fuller's formamide method[15] and used in the dilution which gave maximal precipitation with hyperimmune rabbit serum. The type-specific M extracts, prepared according to Lancefield's technic,[11] were tested for type specificity with absorbed immune rabbit serum of homologous and heterologous types and were proved free of group-specific C substance by the employment of suitable antiserums. The streptococcic nucleoprotein fraction[16] was used in a concentration of 5 mg. of dry weight per cubic centimeter of diluent. The C-reactive protein was determined according to the method of Tillett and Francis[17] with a pneumococcus C polysaccharide[18] in a concentration of 10 mg. per hundred cubic centimeters. The phase precipitin test[19] was performed according to the method of Coburn and Pauli.[20]

The reaction to the bacteriostatic test, previously described,[7d] was considered positive only if there was at least a 2 plus difference in growth from at least two different dilutions as compared with the corresponding streptococcus dilution control.[21]

OBSERVATIONS AND RESULTS

Clinical and Bacteriologic Observations.—A total of 153 patients were studied, 128 males and 25 females. Their ages ranged between 3 and 45 years; 19 patients were in the first decade, 54 in the second,

12. Todd, E. W.: Antigenic Streptococcal Hemolysin, J. Exper. Med. **55**:267, 1932.

13. Hodge, B. E., and Swift, H. F.: Varying Hemolytic and Constant Combining Capacity of Streptolysins: Influence on Testing for Antistreptolysins, J. Exper. Med. **58**:277, 1933.

14. Boisvert, P. J.: The Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940.

15. Fuller, A. T.: The Formamide Method for Extraction of Polysaccharides from Haemolytic Streptococci, Brit. J. Exper. Path. **19**:130, 1938.

16. Lancefield, R. C.: The Immunological Relationships of Streptococcus Viridans and Certain of Its Chemical Fractions: I. Serological Reactions Obtained with Antibacterial Sera, J. Exper. Med. **42**:377, 1925.

17. Tillett, W. S., and Francis, T., Jr.: Serological Reactions in Pneumonia with a Non-Protein Somatic Fraction of Pneumococcus, J. Exper. Med. **52**:561, 1930.

18. With pneumococcus C polysaccharide extract 0.15 cc. of antigen was mixed with an equal volume of undiluted test serum.

19. For the phase precipitin test, 0.1 cc. of antibody serum (phase III serum in acute stage of rheumatic fever) was layered over 0.1 cc. of antigen serum (phase II, prerheumatic or poststreptococcic stage).

20. Coburn, A. F., and Pauli, R. H.: A Precipitinogen in the Serum Prior to the Onset of Acute Rheumatism, J. Exper. Med. **69**:143, 1939.

21. The blood was obtained from children with noninfectious orthopedic disturbances in the New York Orthopedic Hospital, the Hospital for Special Surgery and the New York Hospital through the assistance of Dr. Philip D. Wilson, Dr. Alan De Forest Smith and Dr. S. Z. Levine.

62 in the third, 14 in the fourth and 4 in the fifth. The 153 patients suffered a total of 169 definite hemolytic streptococcic infections of the upper respiratory tract, and in every instance relatively large numbers of hemolytic streptococci, often in almost pure culture, were recovered from the patients' nasopharynxes. Fifty-four different infections were experienced by a group of 39 patients known to have had one or more attacks of rheumatic fever previously; 115 infections occurred among 114 nonrheumatic subjects. In several cases definite clinical evidence of infection was not present, although large numbers of hemolytic streptococci appeared in nose and throat cultures of patients who shortly before had not harbored these micro-organisms and who later had a definite increase of antistreptolysin O. Among the 39 known rheumatic subjects who suffered 54 hemolytic streptococcic infections, there were 17 recurrences of rheumatic fever. Three of these patients each had two separate attacks of rheumatic fever after infections with different types of group A streptococci. Rheumatic fever developed in 21 of the 114 previously nonrheumatic subjects who experienced 115 streptococcic infections. The patients with rheumatic fever had polyarthritis and carditis and at the same time increased leukocyte counts and erythrocyte sedimentation rates; a few patients,[22] however, with accompanying secondary rises in blood leukocyte counts and/or sedimentation rates had only carditis after their streptococcic infections.

Scarlet fever characterized 114 of the 169 infections, but in the following analysis the group with this disease are not differentiated from patients with tonsillitis or pharyngitis without a rash, since many of the patients who in the same epidemic failed to show a rash were infected with the same type of streptococcus as those in whom a scarlatiniform rash developed.

The data given in table 1 show the distribution of the serologic groups and types of streptococci cultured in material from the 153 patients during their 169 attacks of acute pharyngitis; 102 of the attacks were uncomplicated, 29 resulted in purulent complications during the first to the fourth week (average 1.6 weeks) due to the same streptococcic type which caused the initial infection and 38 were followed by acute rheumatic fever. In 4 of these 38 there were also purulent complications. Rheumatic sequelae occurred during the first to the eighth week (average 3.4 weeks) after the onset of the streptococcic infection.

Six of the streptococcic strains belonged to group C, one to group G and one hundred and sixty-two to group A. Twenty-two, or 13.6 per cent, of the group A strains failed to type by the anti-M precipitin method with diagnostic serums representing thirty-seven different serologic

22. Watson, R. F.; Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, J. A. M. A. **128**:1145 (Aug. 18) 1945.

types, although three of these were proved to contain the T antigen of type 14 by the agglutination technic. In 5 instances two types were recovered; the type listed first in table 1 was considered probably responsible for the infection. Type 19 predominated in all three clinical groups and made up 45.3 per cent of the infecting strains of group A streptococci. The preponderance of this type among the patients was due to the inclusion of naval personnel involved in an epidemic of scarlet fever

TABLE 1.—*Serologic Classification of Streptococci Isolated from Patients with Acute Pharyngitis Correlated with the Development of Complications**

		No. of Streptococcic Infections Associated with			Total
		No Complications	Purulent Complications	Rheumatic Fever	
Group A	Type				
	1	3	1	1	5
	3	9	1	1	11
	3-14†	1			1
	5	1			1
	6	5	2	2	9
	6-14†		1		1
	12	2			2
	14	3		2	5
	17	3	2	2	7
	18	2			2
	19	38	13	17	68
	19-6†	1	1	1	3
	23	1	1		2
	26	2	1	3	6
	29	1			1
	30	6	2		8
	32			1	1
	33	1		1	2
	38	3			3
	39	1			1
	45	1			1
	NC‡	11	4	7	22
Group C		6			6
Group G		1			1
	Totals	102	29	38	169

*A total of 153 patients suffered 169 different streptococcic infections.
†Streptococci of two types were recovered from these patients. The type listed first was considered probably responsible for the infection.
‡These strains could not be classified into types by the precipitin technic, but one in the group with no complications and two in the group with purulent complications were proved by the agglutination method to contain the T antigen of type 14.

previously reported.[23] It is of interest to note, however, that nine other serologic types, as well as seven unclassified strains, caused infections that were followed by rheumatic fever

It is also of interest that the 7 hemolytic streptococcic infections not of group A were not followed by rheumatic fever although 5 of them occurred in patients who were known to have had rheumatic fever previously and who were therefore presumably susceptible to the disease.

23. Watson, R. F.; Schwentker, F. F.; Fetherston, J. E., and Rothbard, S.: Sulfadiazine Prophylaxis in an Epidemic of Scarlet Fever, J. A. M. A. **122**:730 (July 10) 1943.

In fact, in 1 of these rheumatic subjects a recurrent attack of rheumatic fever subsequently developed after a group A streptococcic infection. It is significant that no single serologic type of group A streptococci could be correlated with the development of either purulent complications or rheumatic fever. The distribution of the various serologic types was approximately the same in patients who made uneventful recoveries as in those in whom complications or sequelae developed.

Antibody Studies.—A summary of the results of the antistreptolysin O titrations and the antifibrinolysin determinations made on the serums and plasma respectively of the patients without complications and of those who suffered purulent complications or rheumatic fever after

TABLE 2.—*Summary of Weekly Determinations of Antistreptolysin O and Antifibrinolysin Correlated with the Type of Clinical Reaction to Streptococcic Infections*

Complications and Sequelae		None	Purulent	Rheumatic Fever	Total
ANTISTREPTOLYSIN O					
Number of infections		102	29	38	169
Increased titers:	Number	78	22	32	132
	Per cent	76.4	75.9	84.2	78.1
Beginning of rise*	Weeks	2.1	2.2	2.0	2.2
Maximal level*	Weeks	4.7	3.9	5.5	4.8
Maximal level (units/cc.)† / Initial level (units/cc.):	Ratio	3.8	9.3	5.1	5.0
ANTIFIBRINOLYSIN					
Number of infections		85	26	24	135‡
Increased titers:	Number	46	17	19	82
	Per cent	54.1	65.4	79.2	60.1
Beginning of rise*	Weeks	2.5	2.7	2.4	2.5
Maximal level*	Weeks	3.4	3.2	3.0	3.2

*Based on average time in weeks after onset of infection.
†An expression of the magnitude of the response, based on the average of the ratios $\frac{\text{maximal level}}{\text{initial level}}$ calculated for each individual patient.
‡In an additional 34 infections (20 per cent) antifibrinolysin determinations could not be made because of high or maximal resistance of the plasma clot to fibrinolysis at the onset of infection.

streptococcic pharyngitis is presented in table 2. The data cover all the determinations made at the time of the acute streptococcic infection and weekly thereafter until the patients were discharged from the hospital. In some instances, further determinations were made from blood samples obtained on subsequent visits to the clinic at three to four week intervals.

A significant increase in the serum antistreptolysin O titer was considered to have occurred only if it increased by two or more dilutions over that shown at the time of the initial determination. In accordance with this criterion, the serum antistreptolysin O titer increased in 76.4 per cent of the patients with uncomplicated pharyngitis, in 75.9 per cent of those in whom purulent complications developed and in 84.2 per cent of those in whom rheumatic fever developed (table 2). The

interval between the onset of infection and the beginning of the rise in the antistreptolysin O titer was essentially the same for the three groups, namely, 2.1, 2.2 and 2.0 weeks respectively. The average interval between the onset of infection and the time at which the maximal titer was reached was 4.7 weeks for the patients with no complications, 3.9 weeks for the patients in whom purulent complications developed and 5.5 weeks for those in whom rheumatic fever developed. In table 2 the magnitude of the serum antistreptolysin O response is expressed as the ratio between the maximal and the initial titers. When the responses of these three groups of patients are compared on this basis, it is evident that the average rise was 9.3 times for the group of patients in whom purulent complications developed, 5.1 times for those in whom rheumatic fever developed and only 3.8 times for those who had no complications. The data seem to indicate that, on the average, patients in whom rheumatic fever develops are more likely to have significant serum antistreptolysin O responses, with slightly delayed maximal titer, and are also likely to have a more intense response than the patients with uncomplicated disease but a less intense response than those who suffer purulent complications. These results, however, are of doubtful significance since the groups studied are small. Moreover, when the individual patients are considered, it is found that there is great variation and considerable overlapping among the members of the three groups.

A total of 132 (78 per cent) of the 169 streptococcic infections resulted in significant rises in the antistreptolysin O titer. The average time for the beginning of the rise in titer was 2.2 weeks; for the maximal level to be reached, 4.8 weeks were required. The average maximal-initial ratio was 5.0 times.

The antifibrinolysin was considered significantly increased only if between admission and discharge there was an increase of 2 plus in the results. These tests were less satisfactory for comparison than were the determinations of antistreptolysin O because this test, as employed here, was not quantitative[24] and in many instances increase in antifibrinolysin could not be measured because the initial level was too high. Even though the numbers are small, it is noteworthy (table 2) that 79.2 per cent of the patients in whom rheumatic fever developed showed a significant increase in their antifibrinolysin titers whereas only 54.1 per cent of the group without complications and only 65.4 per cent of the patients in whom purulent complications developed showed increased titers. The average time of onset of the initial increase in resistance to lysis of the plasma clot and the time when the maximal level was reached were essentially the same for each group.

24. Since these tests were made, Kaplan has recently devised a quantitative serologic method for the estimation of serum antifibrinolysin which possesses a number of advantages over the plasma test (Kaplan, M. H.: J. Clin. Investigation **25**:347, 1946).

In a total of 83 (60 per cent) of 135 infections significant increases in the antifibrinolysin titers were observed. The beginning of the rise of antifibrinolysin and the maximal level occurred in 2.5 and 3.2 weeks respectively. Unfortunately, it was not possible to determine the duration of the increase of either antistreptolysin O or antifibrinolysin because many patients were discharged from the hospital before the antibody responses returned to the initial level.

Additional Antibody Studies.—From the entire group of 153 patients, 71 who suffered 83 different group A streptococcic infections were selected for a more comprehensive study of their antibody responses. These patients were divided into three groups, on the basis of their clinical response to the streptococcic infections, in the same manner in which the large group was considered, namely, (1) those in whom complications failed to develop, (2) those in whom purulent complications developed and (3) those in whom rheumatic fever developed. In addition to determinations of antistreptolysin O and antifibrinolysin, the serums of these patients were tested at weekly intervals for the presence of streptococcic bacteriostatic antibodies and precipitins directed toward the type-specific M protein, the group-specific C carbohydrate and a nucleoprotein fraction of group A streptococci and for the presence of C-reactive protein (against pneumococcus C).

In table 3 are summarized the findings with respect to four different streptococcic antibodies which developed in these 71 patients. The results of the antistreptolysin O titrations for these three groups are essentially the same as those found for the three larger groups and recorded in table 2. The percentage of patients who showed increased antifibrinolysin titers is somewhat higher than that in the larger group. This slight difference is probably due to the difference in the number of cases summarized in the two tables. Because larger groups tend to be more representative, we believe that the figures given in table 2 reflect more accurately the comparative differences between the three groups of patients than those in table 3.

The bacteriostatic and anti-M precipitin tests were employed to determine the presence of type-specific antibodies in the serums of these patients; the results are recorded in table 3. Eighty-eight per cent of the patients in whom rheumatic fever developed had demonstrable type-specific bacteriostatic antibodies, whereas 69 per cent of those with purulent complications and 67 per cent of those without any complications had them. In general, in the patients in whom rheumatic fever developed there was also a slight delay in the appearance of the bacteriostatic antibodies as compared with the two other groups of patients: the individual values, however, spread widely about the average, and some patients (table 3) in whom rheumatic fever developed showed a

bacteriostatic antibody response as early as did those in whom rheumatic fever failed to develop after their streptococcic infection. In general the period for which these antibodies lasted could not be determined because they were still present when the patients left the hospital. In most instances, however, they persisted for at least many months and in some for over two years.

TABLE 3.—*Summary of Weekly Determinations of Different Streptococcic Antibodies Correlated with the Type of Clinical Reaction to Streptococcic Infections*

Complications and Sequelae		None	Purulent	Rheumatic Fever*	Total
ANTISTREPTOLYSIN O					
Number of infections		33	16	34	83
Increased titers:	Number	23	12	29	64
	Per cent	69.7	75.0	85.3	77.1
Beginning of rise†	Weeks	2.4	2.3	2.0	2.4
Maximal level†	Weeks	4.8	3.8	5.8	5.3
Maximal level (units/cc.)‡ / Initial level (units/cc.):	Ratio	4.2	10.6	5.4	6.0
ANTIFIBRINOLYSIN					
Number of infections		27	15	21	63**
†Increased titers:	Number	17	12	17	46
	Per cent	62.9	80.0	80.9	73.0
Beginning of rise†	Weeks	3.1	2.5	2.3	2.6
Maximal level†	Weeks	4.2	3.2	3.0	3.5
BACTERIOSTATIC ANTIBODIES					
Number of infections		33	16	33	82
Increased titers:	Number	22	11	29	62
	Per cent	66.7	68.8	87.9	75.6
Beginning of rise†	Weeks	4.2	3.9	6.1	5.1
Range†	Weeks	2 to 10	2 to 8	1 to 13	
ANTI-M PRECIPITINS					
Number of infections		33	16	34	83
Increased titers with:					
(1) Homologous M antigen	Number	15	9	29	53
	Per cent	45.5	56.2	85.3	63.9
(2) Heterologous M antigens¶	Number	10	7	22	39
	Per cent	33.3	43.8	61.8	46.9
Beginning of rise†	Weeks	3.6	2.6	6.0	4.8
Range†	Weeks	1 to 8	1 to 5	1 to 23	

*Four of these patients also had purulent complications.
†Based on average time in weeks after onset of infection.
‡An expression of the magnitude of the response; based on the average of the ratios $\frac{\text{maximal level}}{\text{initial level}}$ calculated for each individual patient.
**In an additional 20 infections, determinations of antifibrinolysin could not be made because of high or maximal resistance of the plasma clot to fibrinolysis at onset of infection.
¶Reactions were usually observed with heterologous M antigens in serums which also gave reactions with homologous M antigens.

Although the results of the bacteriostatic test were strikingly type specific, the precipitin reactions with homologous and heterologous M extracts showed little evidence of type specificity. The highest incidence (85.3 per cent) of positive reactions, however, was again found in patients in whom rheumatic fever developed, and the average time of appearance of these antibodies was delayed as compared with that in the other two groups. However, as shown in table 3, cross reactions with

heterologous M extracts were so frequent that little reliance can be placed on the type specificity of the test. Among the patients tested, with a total of 83 infections, 53 showed reactions with homologous M extracts, but 39 of the 53, or 73.6 per cent, showed equally strong reactions with extracts of heterologous types. Furthermore, the serums which reacted with heterologous type extracts usually reacted as well with the homologous type extracts. The results probably can be interpreted best as evidence of response to non-type-specific streptococcic products.

The group-specific carbohydrate C antibody was found in only 5 of the 83 infections; four of the positive reactions occurred with serums of patients in whom attacks of rheumatic fever developed and one with the serum of a patient in whom a suppurative complication developed. The precipitin directed against the nucleoprotein fraction was detected in only 3 patients, in all of whom rheumatic fever developed. In these 3, antibodies against both group-specific C carbohydrate and the nucleoprotein fraction were observed.

The C-Reactive Protein.—This protein, contained in the alpha$_1$ globulin fraction,[25] is precipitated with dilute solutions of pneumococcus "C" polysaccharide and is found in the serum during the acute phase of various infectious diseases.[26] Although C-reactive protein is apparently in no way related to the formation of antibodies, it seemed of interest to compare its occurrence and duration in the presence of complications and sequelae following group A streptococcic infections in rheumatic and nonrheumatic subjects.

The results shown in table 4 indicate that the C-reactive protein was observed in 63, or 75.9 per cent, of the 83 infections. In patients showing positive reactions, it was usually detected in the serums obtained during the acute streptococcic phase and during the time of purulent complication as well as in the period of greatest rheumatic activity. It occurred in 51.4 per cent of the patients without complications, in 75 per cent of those with purulent complications and in 97.6 per cent of those in whom rheumatic fever developed.[27] The presence of the C-reactive protein in

25. Perlman, E.; Bullowa, J. G. M., and Goodkind, R.: An Immunological and Electrophoretic Comparison of the Antibody to C Polysaccharide and the C Reactive Protein of Acute Phase Serum, J. Exper. Med. **77**:97, 1943.

26. Ash, R.: Non-Specific Precipitins for Pneumococcic Fraction C in Acute Infections, J. Infect. Dis. **53**:89, 1933. Abernethy, T. J., and Avery, O. T.: The Occurrence During Acute Infections of a Protein Not Normally Present in the Blood: I. Distribution of the Reactive Protein in Patients' Sera and the Effect of Calcium on the Flocculation Reaction with C Polysaccharide of the Pneumococcus, J. Exper. Med. **73**:173, 1941. Tillett and Francis.[17]

27. These percentages would probably have been increased if antiserum prepared in rabbits to C-reactive protein from human sources (Macleod, C. M., and Avery, O. T.: J. Exper. Med. **73**:191, 1941) had been used instead of the "C" polysaccharide.

the serums showed a close correlation with the intensity and duration of the inflammatory reaction of the host, as indicated by the elevated temperatures and increased serial erythrocyte sedimentation rates illustrated in charts 1, 2, 3 and 4. This protein persisted longest in the serums of patients with rheumatic fever.

Phase Precipitins.—Escherich and Schick,[28] Schlesinger[29] and Coburn and Pauli[30] described three different clinical phases in the development of rheumatic fever. Phase I represents the acute streptococcic infection, phase II an afebrile and often asymptomatic period and phase III the state of rheumatic fever. A precipitation reaction which sometimes occurs when serums taken in phase II and phase III are mixed has been described by Coburn and Pauli.[20] The serum in phase II was considered by them to contain an antigen and that taken in phase III

TABLE 4.—*Summary of Weekly Determinations of the C-Reactive Protein in Patients with Different Types of Clinical Reactions to Streptococcic Infections*

Complications and Sequelae		None	Purulent	Rheumatic Fever	Total
Number of infections		33	16	34	83
Positive reactions	Number	18	12	33	63
	Per cent	51.4	75.0	97.6	75.9

an antibody. These authors recorded no precipitate obtained by mixing phase I and phase II serums or phase I and III serums.

Wedum and Wedum[31] observed phase precipitin reactions not only with serums from patients with rheumatic fever but also with those from patients with atypical pneumonia and nasopharyngitis, and occasionally with those from apparently normal blood donors.

In the present study, serums which were obtained from 9 patients in all three phases in the evolution of their attacks of rheumatic fever were tested for phase precipitins. In certain cases faint rings were observed at the interface of the two serums, but this occurred as often between the serums obtained in phases I and II or phases I and III as it did between phase II and phase III serums. In other cases no rings or precipitates were observed. It is not clear whether these faint rings represented true precipitin reactions.

28. Escherich, T., and Schick, B., Scharlach, Vienna, A. Hölder, 1912.

29. Schlesinger, B.: The Relationship of Throat Infection to Acute Rheumatism in Childhood, Arch. Dis. Childhood **5**:411, 1930.

30. Coburn, A. F., and Pauli, R. H.: Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process: III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, J Exper. Med. **56**:651, 1932.

31. Wedum, A. G., and Wedum, B. G.: Serum Precipitation Reaction in Rheumatic Fever and in Other Conditions, Proc. Soc. Exper. Biol. & Med. **61**:432, 1946.

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Details of Findings in Typical Patients.—In charts 1, 2, 3 and 4 are shown the clinical course of 4 typical patients and the corresponding serologic and bacteriologic studies done. Chart 1 shows the course of a patient who made an uneventful recovery, chart 2 illustrates the observations made on a patient in whom a purulent complication developed, chart 3 illustrates the course of a patient in whom a primary attack of rheumatic fever developed after a streptococcic infection and chart 4 shows the observations made on a rheumatic subject with 3 different group A streptococcic infections of the upper respiratory tract. The first

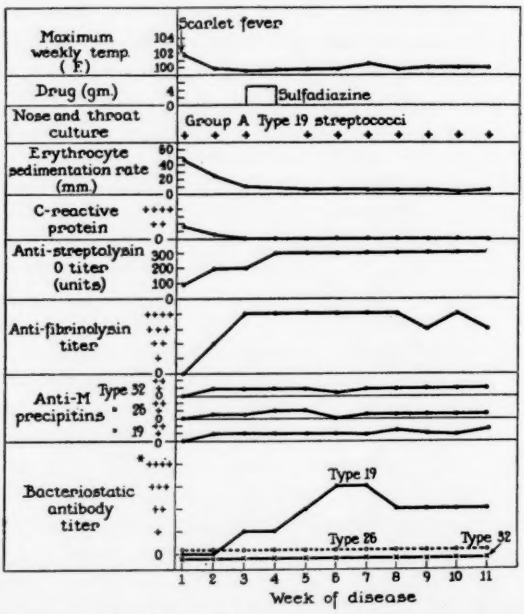

Chart 1.—Course of a patient with an uncomplicated streptococcic infection of group A type 19.

*+, ++ and +++ represent significant bacteriostasis of streptococci in culture dilutions of 10^{-6}, 10^{-5} and 10^{-4} respectively; 10^{-6} usually represented 200 to 300 colonies per cubic centimeter.

infection in the last patient was uncomplicated, but the second and third resulted in recurrent attacks of rheumatic fever. Certain points are noteworthy in all these charts: (1) the persistence of hemolytic streptococci in the nasopharynxes of the patients; (2) the close correlation of the increased erythrocyte sedimentation rates with the presence of the C-reactive protein in the serum; (3) the cross reactions with the type-specific M protein extracts; (4) the type specificity of the bacteriostatic test and the long period for which the bacteriostatic antibodies

were present, and (5) the special importance of the determinations of antistreptolysin O and the bacteriostatic tests in patients with reinfection by different serologic types of group A streptococci.

Multiple Streptococcic Infections.—In 11 of the 153 patients more than one group A streptococcic infection developed. Ten were known

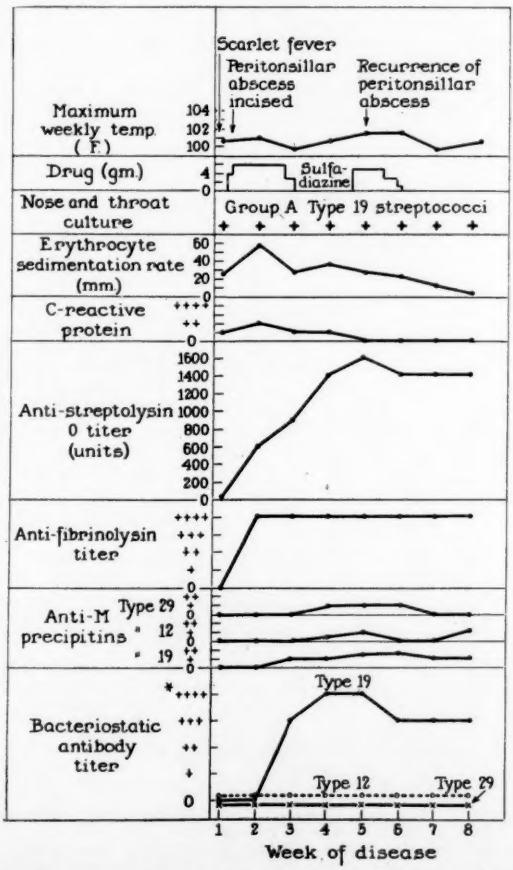

Chart 2.—Course of a patient with a purulent complication following group A type 19 streptococcic infection.

*+, ++, +++ and ++++ represent significant bacteriostasis of streptococci in culture dilutions of 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} respectively; 10^{-6} usually represented 200 to 300 colonies per cubic centimeter.

rheumatic subjects, and 1 was a normal sibling of a brother with rheumatic disease. In 3 of the patients 3 separate infections developed, and 2 developed in 8 others. In 10 of the patients different known types of hemolytic streptococci were cultured from the nasopharynxes in each infection, but in 1 patient with three separate attacks of disease of

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the upper respiratory tract the streptococci could not be typed with the available serums by the precipitin technic although there were definite clinical findings and antibody responses in each of these infections. However, during 1 of the 3 infections, an indication was obtained that the strain was different from the others because bacteriostatic antibodies specific for this strain appeared in the patient's serum. The patients

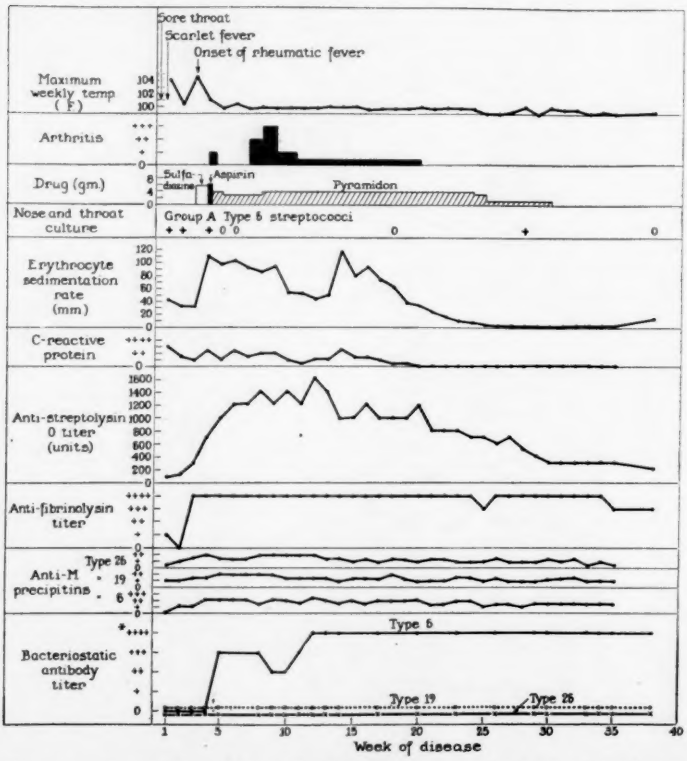

Chart 3.—Course of a patient who had a primary attack of acute rheumatic fever after a group A type 6 streptococcic infection.

*+, ++, +++ and ++++ represent significant bacteriostasis of streptococci in culture dilutions of 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} respectively; 10^{-6} usually represented 200 to 300 colonies per cubic centimeter.

with multiple but separate infections of the respiratory tract had a different type of streptococci with each infection.

Of primary interest also in this study is the fact that many of the rheumatic subjects suffered a number of nonstreptococcic infections such as rubella, herpes zoster, bacillary dysentery, appendicitis, acute epidemic conjunctivitis (pink eye), pneumococcic pneumonia and infections

of the upper respiratory tract of unknown origin, but in no instance was rheumatic fever observed after these infections. In this respect our findings are in agreement with those of others.[32]

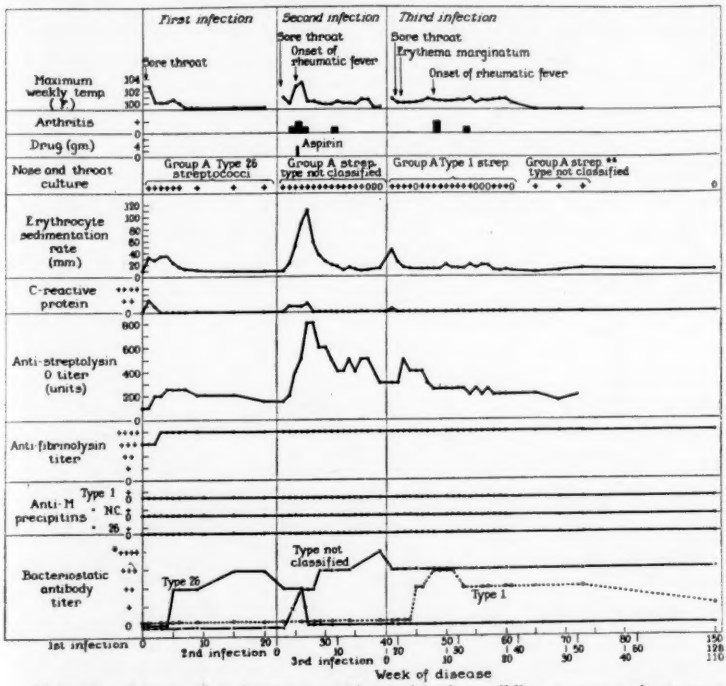

Chart 4.—Course of a rheumatic subject with three different group A streptococcic infections.

*+, ++, +++ and ++++ represent significant bacteriostasis of streptococci in culture dilutions of 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} respectively; 10^{-6} usually represented 200 to 300 colonies per cubic centimeter.

**The streptococci of unclassified type comprised only a few colonies and were probably the same as those which caused the second infection.

COMMENT

In order to determine whether there is any basic difference in the patterns of streptococcic antibodies in patients in whom rheumatic fever develops as compared with those who have purulent complications or

32. Reyersbach, G.; Lenert, T. F., and Kuttner, A. G.: An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis: Clinical and Epidemiological Observations, J. Clin. Investigation **20**:289, 1941. Green, C. A.: Epidemiology of Haemolytic Streptococcal Infections in Relation to Acute Rheumatism: III. Comparative Incidence of Various Infections and Acute Rheumatism in Certain Training Centers, J. Hyg. **42**:380, 1942. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945.

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make uneventful recoveries after hemolytic streptococcic infections of the upper respiratory tract, the immunologic responses to a variety of antigens were studied in fairly large groups of patients. It is well known[33] that different strains and serologic types of streptococci vary in their antigenic composition and thus they may evoke different responses in the host. Moreover, persons are also known to respond differently to the same antigen.

The antistreptolysin O test gives the most satisfactory index of previous streptococcic infections, probably because streptolysin O is an excellent antigen and the titer of this antibody can be accurately determined. The determinations of antifibrinolysin in this study were done before the quantitative method recently described by Kaplan[24] had been devised, and quantitative results were therefore not obtained. Because of its simplicity, it was hoped that the anti-M precipitin test could be used for determinations of type-specific antibodies. It was found, however, that frequent and marked cross reactions with heterologous M extracts made this test an unreliable index of type specificity in patients' serums. Similar difficulties were encountered by Thomas.[34] These reactions were not due to the group-specific C carbohydrate because this antigen had been eliminated from the M extracts. At present, the nature of these cross reactions is not understood, and the precipitin test as performed probably did not give a reflection of the type-specific antibodies in the patients' serums. The most reliable method for determining such antibodies was found to be the bacteriostatic test. In contrast to the anti-M precipitin test, no cross reactions were observed.

Since the antistreptolysin O reaction is the most sensitive test now available for detecting previous streptococcic infection, it was thought of interest to find out how often a rise in antistreptolysin O was accompanied with antifibrinolysin, bacteriostatic and anti-M precipitin responses. The data, obtained on 71 patients who had 83 group A strep-

33. Bailey, J. H.: The Types of Hemolytic Streptococci Found in Scarlet Fever Patients and in Throats of Grammar-School Children, Am. J. Hyg. **29**:107, 1939. Colebrook, L.; Elliott, S. D.; Maxted, W. R.; Morley, C. W., and Mortell, M.: Infection by Non-Hemolytic Group A Streptococci, Lancet **2**:30, 1942. Lancefield, R. C., and Stewart, W. A.: Studies on the Antigenic Composition of Group A Hemolytic Streptococci: II. The Occurrence of Strains in a Given Type Containing M but No T Antigen, J. Exper. Med. **79**:79, 1944. Herbert, D., and Todd, E. W.: The Oxygen-Stable Haemolysin of Group A Haemolytic Streptococci (Streptolysin S), Brit. J. Exper. Path. **25**:242, 1944. Studies on Streptococcal Fibrinolysis. V. The in Vitro Production of Fibrinolysin by Various Groups and Types of Beta Hemolytic Streptococci; Relationship to Antifibrinolysin Production, Commission on Acute Respiratory Diseases, J. Exper. Med. **85**:441, 1947.

34. Thomas, R. A.: Precipitation and Agglutination Tests with the Hemolytic Streptococcus: Titration of "M" and "T" Anti-bodies in Human Sera, Science **100**:552, 1944.

tococcic infections, are summarized in table 5. Sixty-four of the 83 infections (77 per cent) induced a significant rise in the antistreptolysin O titer. During 14 of these 64, it was impossible to learn whether additional antifibrinolysin appeared because of the limitations of the method used; a rise in antifibrinolysin was observed during 40 of the remaining 50. In 45 of the 64 there was a rise in bacteriostatic antibodies. In 42 anti-M precipitins developed, but the significance of this finding is not clear, since in 32 of these cross reactions were observed. On the other side of the picture, in 16 of the 19 infections in which antistreptolysin O was not increased there was a rise in the bacteriostatic antibodies; in 1 of the remaining 3 there was an antifibrinolysin response, and in 2 anti-M precipitins developed. From these results it can be seen that antibodies directed against one or several of the various antigenic components of group A streptococci appeared in the serums of all the patients after the infection. Moreover, in 50.5 per cent of the

TABLE 5.—*Correlation of the Antistreptolysin O Response with Antifibrinolysin, Bacteriostatic and Anti-M Precipitin Reactions in Serums from Patients with 83 Group A Streptococcic Infections of the Upper Respiratory Tract*

Antistreptolysin O	Positive 64			Negative 19		
	Positive	Negative	Not Determined	Positive	Negative	Not Determined
Antifibrinolysin	40	10	14	6	7	6
Bacteriostatic antibodies	45	19	..	16	2 (1)*	..
Anti-M precipitins	42 (32)†	22	..	11 (7)†	8	..

*Figure in parentheses indicates that in one additional infection bacteriostatic antibodies could not be determined because streptococci isolated from the patient did not grow in whole blood of normal children even without addition of test serum.

†Figures in parentheses indicate the number in which reactions with heterologous M antigens were also present.

83 infections three different antibodies, directed against streptolysin O, fibrinolysin and the type-specific M protein, appeared in the patients' convalescent serums.

Our findings are in accord with those of previous observers, who found that group A streptococcic infections of the upper respiratory tract precede the development of rheumatic fever. By means of immunologic studies, it is usually possible to establish the cause of the precursory pharyngitis in rheumatic patients as group A streptococci, although these micro-organisms may not be found on culture; the chances of obtaining this positive immunologic evidence are increased in proportion to the number of different antibody tests applied.

A comparison of the immune responses of the patients in whom rheumatic fever developed with those of the ones who escaped complications or sequelae or in whom purulent complications developed shows

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that antistreptolysin O, antifibrinolysin, anti-M precipitins and type-specific bacteriostatic antibodies developed more frequently in rheumatic patients than in nonrheumatic ones. In the rheumatic group the maximal response of antistreptolysin O and the type-specific bacteriostatic antibody was delayed about two weeks as compared to that in the other two groups. When the average weekly bacteriostatic antibody responses of the rheumatic and nonrheumatic groups were reviewed, the former had an average lower response than the latter during each of the second to the fifth weeks. Whether these differences have significance with respect to the pathogenesis of rheumatic fever cannot at present be stated.

Mote and Jones[1c] found that, compared to patients with streptococcic infections who recovered without sequelae, patients who had purulent complications as well as those in whom rheumatic fever developed exhibited a delay in the rise of antistreptolysin O. Coburn[6b] also found a delayed antistreptolysin O response in patients in whom rheumatic fever developed after streptococcic infections of the upper respiratory tract, and he stated that this is characteristic. Because the grouping of our cases was not the same as that of these authors, direct comparison is not possible. In our series the beginning of the rise of antistreptolysin O was not delayed. These results are similar to those obtained by Kuttner and Krumwiede.[10] In our patients the maximal response occurred later in the rheumatic group than in the nonrheumatic group. Since the difference was not great and the number of patients in each group was small and since there were great individual variations within each group, it cannot be concluded from this study that a delayed appearance of antistreptolysin O is characteristic of the rheumatic patient.

Swift and Hodge[6a] and Coburn[6b] also reported a delayed response of anti-M precipitins in patients in whom rheumatic fever develops. The precipitin reactions which we obtained with M extracts and patients' serums were similar to those reported by these authors; however, in view of the numerous cross reactions observed, the significance of this reaction is not clear. On the other hand, the delayed response of the bacteriostatic antibodies, which is type specific, may be significant. As previously indicated, this applies to groups and not to individuals.

One of three factors may be invoked to explain the difference between rheumatic and nonrheumatic groups of patients.

1. The groups are too small and the differences too slight to have significance.

2. The administration of salicylates to the rheumatic patients may have delayed formation of the type-specific antibodies.

3. The average statistical differences may indicate that it is part of the nature of rheumatic fever to have a delayed type-specific streptococcic antibody response to group A streptococcic infections.

Several previous investigations indicate that salicylates may depress the formation of antibodies.[35] In the present study, however, if salicylates had had this effect in the rheumatic group who had received them, it probably would have been reflected in the production of antistreptolysin O and antifibrinolysin as well as of anti-M precipitins and bacteriostatic antibodies (table 3). This was not the case, for the production of antibodies was greatest in the rheumatic group. The lag was evident only in the formation of type-specific antibodies. It should also be noted that salicylates were not given to the rheumatic patients until the third to the fifth week after the onset of the streptococcic infections; hence the conditions were different from those in the aforementioned investigations.[35] The observations would have been better controlled if a rheumatic group who were not receiving salicylates had been utilized, but for obvious reasons this was impractical.

Such suggestions, as the figures herein presented may indicate, could only be brought out from an analysis of groups and not from the findings in any one person, especially when the manifestations of rheumatic fever may appear any time within a period of one to eight weeks after the precursory streptococcic infection. Possibly with the development of further knowledge of streptococcic antigens and of new technics, these suggestions will lead to further exploration.

SUMMARY AND CONCLUSIONS

1. One hundred and sixty-nine acute hemolytic streptococcic infections of the upper respiratory tract in 153 rheumatic and nonrheumatic patients were studied.

A. Group A streptococci caused 163 of these infections, group C caused 6 and group G caused 1. No cross infections occurred, and in no case did the same serologic type of group A streptococcus cause two separate infections in the same patient.

B. One hundred and two of the infections were uncomplicated, 29 were followed by purulent complications due to the same strain causing the original infection and 38 were followed by rheumatic fever. Four of these 38 were also followed with purulent complications.

C. Rheumatic recurrences developed seventeen times (31.4 per cent) as a result of 54 streptococcic infections in 39 previously rheumatic subjects. On the other hand, primary attacks of rheumatic

35. Swift, H. F.: The Action of Sodium Salicylate upon the Formation of Immune Bodies, J. Exper. Med. **36**:735, 1922. Derick, C. L.; Hitchcock, C. H., and Swift, H. F.: The Effect of Anti-Rheumatic Drugs on the Arthritis and Immune Body Production in Serum Disease, J. Clin. Investigation **5**:427, 1928. Homburger, F.: Sodium Salicylate Inhibiting Anti-Rh Immunization in Animals, Proc. Soc. Exper. Biol. & Med. **61**:101, 1946.

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fever resulted from 21 (18.3 per cent) of the 115 streptococcic infections suffered by 114 previously nonrheumatic subjects.

D. Rheumatic manifestations followed only those infections of the upper respiratory tract which were due to group A hemolytic streptococci; among these no special serologic type of streptococcus was found associated either with rheumatic fever or with purulent complications of the original infections. None of the 7 infections due to streptococci of groups C and G led to rheumatic sequelae, although 5 of these occurred in patients who had previously had rheumatic fever.

2. Determinations of antistreptolysin O and antifibrinolysin were done weekly on all patients. Seventy-one of these patients (with 83 infections) were tested for other immune responses, i.e., type-specific bacteriostatic antibodies and precipitins against type-specific M, group-specific C and streptococcic nucleoprotein. The serums of these 71 patients were also tested for C-reactive protein, and serums from 9 patients with rheumatic fever were examined for "phase" precipitins.

A. Significant rises of antistreptolysin O occurred in 77 per cent, of antifibrinolysin in 73 per cent, of bacteriostatic antibodies in 76 per cent, of anti-M precipitins in 64 per cent and of C-reactive protein in 71 per cent of the 83 infections. Similar results were obtained for the antistreptolysin O and antifibrinolysin titers of patients in the complete series of 153. No definite phase precipitins could be demonstrated in the 9 patients examined. Three different streptococcic antibodies were demonstrable in the serum of 50 per cent of the patients in the series of 83 infections, and one or more of the several antibodies investigated were found during convalescence in every patient.

B. The patients with rheumatic fever as a group exhibited rises in antistreptolysin O, antifibrinolysin and type-specific antibodies more frequently than did the group of patients who had purulent complications or who made uneventful recoveries. Patients with purulent complications, however, exhibited the greatest increases in antistreptolysin O titer.

C. A slight delay in the beginning of the rise of type-specific bacteriostatic antibodies and anti-M precipitins, as well as a similar delay until the maximal level of antistreptolysin O was reached, was observed in the group of patients with rheumatic fever as compared with the nonrheumatic groups.

3. From this study it is evident that at present no single pattern of antibody response can be used to diagnose the existence of rheumatic fever in any single person.

THYMOL TURBIDITY TEST IN ACUTE INFECTIOUS DISEASES

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AND
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IN 1944 MacLagan[1] introduced the thymol turbidity test for diagnosis of diseases of the liver. With this test it should be possible to distinguish between hepatitis, obstructive jaundice and hepatic cancer. The thymol turbidity test has since been analyzed by various investigators (Watson and Rappaport,[2] Hawkinson and Giebenhain, Shank and Hoagland,[3] Kunkel and Hoagland,[4] Lehmann,[5] Maizels,[6] Havens and Marck[7] and Brante[8]). In conformity with MacLagan these investigators observed the reaction to be positive in about 90 per cent of cases of acute hepatitis and as a rule positive in chronic hepatitis, whereas it was rarely observed to be positive in cases of obstruction of the bile duct and hepatic cancer.

The thymol turbidity test is a flocculation reaction on certain plasma proteins. The flocculation occurs by means of a saturated thymol solution at *p*H 7.8. The turbidity is read in Pulfrich's photometer against a barbital buffer solution with thymol. The result may be indicated by the extinction value or converted into MacLagan's units.

The basis of the thymol test is by no means clear. Various writers have held that the positive reaction is due to certain changes in the serum globulin fraction, presumably the gamma globulin. These changes need not, however, be quantitative (MacLagan,[9] Kabat, Hanger, Moore

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From the Department of Infectious Diseases, Frederiksberg Hospital (Physician in Chief N. I. Nissen, M.D.), Copenhagen.

1. MacLagan, N. F.: Brit. J. Exper. Path. **25**:234, 1944.
2. Watson, C. J., and Rappaport, E. M.: J. Lab. & Clin. Med. **30**:983, 1945.
3. Shank, R. E., and Hoagland, C. L.: J. Biol. Chem. **162**:133, 1946.
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5. Lehmann, J.: Nord. med. **25**:1364, 1946.
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7. Havens, W. P., and Marck, R. E.: J. Clin. Investigation **25**:816, 1946.
8. Brante, G.: Svenska läk. tidskr. **43**:2661, 1946.
9. MacLagan, N. F.: Nature, London **154**:670, 1944.

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and Landow[10] and Brante[8]). By examining the thymol precipitate MacLagan[1] observed it to be a protein-thymol-phospholipid complex. The thymol reactions became negative by ether extraction of the plasma. This fact lends support to the view that the reaction may be due to changes in the lipid content of the plasma or in the lipid-protein complex. Recant, Chargaff and Hanger[11] concluded from their experiments that a positive reaction to a thymol test is conditioned by an increased lipid content in the plasma, whereas the gamma globulin should play an inferior part.

The fact that possible changes in the gamma globulins of serum might determine the result of the thymol test gave rise to the present investigation of the thymol test in acute virus diseases. Treatment of measles

Fig. 1.—Results of the thymol turbidity test in 88 normal persons, 33 male and 55 female. (Abscissa: the extinction value; ordinate: number of normal persons.)

with gamma globulin during the incubation and at the initial stage of the disease is known to be able to alleviate or totally prevent the onset (Ordman, Jennings and Janeway[12] and Stokes, Maris and Gellis[13]). It has likewise been possible to reduce the incidence of the complicating orchitis in mumps by administration of gamma globulin extracted from serums of convalescent patients (Gellis, McGuinness and Peters[14]).

In addition to throwing light on these problems the present investigation gives information of the specificity of the thymol test and contributes to an elucidation of its value as a test of hepatic function.

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10. Kabat, E. A.; Hanger, F. M.; Moore, D. H., and Landow, H.: J. Clin Investigation **22**:563, 1943.

11. Recant, L.; Chargaff, E., and Hanger, F. M.: Proc. Soc. Exper. Biol. & Med. **60**:245, 1945.

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14. Gellis, S. S.; McGuinness, A. C., and Peters, M. A.: Am. J. M. Sc. **210**:661, 1945.

INVESTIGATIONS

Our material was composed of a collection of normal persons and of patients, the latter nearly all patients with acute infectious diseases admitted to the department for infectious diseases in the course of six months.

The normal series comprised 88 normal subjects (55 women and 33 men). None of these had had hepatitis or recently any other infectious diseases.

Figure 1 illustrates the distribution of thymol analyses concerning the 88 normal subjects. The diagram is peculiar in having two peaks, one at an extinction value of about 0.07 and one at about 0. This leads to the supposition that a number of the values observed to be about 0 should actually have been negative.

The theoretic distribution curve corresponding to the present material has been plotted (fig. 1). The mean value was observed to be 0.08

TABLE 1.—*Thymol Turbidity Test in Different Acute Infectious Diseases*

Diagnosis	No. of Cases	No. with Positive Reactions	Percentage with Positive Reactions
Measles	45	32	71.0
Infectious mononucleosis	34	25	73.5
Tonsillitis	82	9	11.0
Streptococcic tonsillitis	29	4	13.8
Nonstreptococcic tonsillitis	53	5	9.5
Scarlet fever	73	4	5.5
Acute epidemic parotitis	31	2	6.5
Serous meningitis of unknown origin	47	2	4.3
Smallpox	5	1	
Erythema multiforme	2	1	
Atypical exanthema	3	0	
Pneumonia	14	0	
Acute infectious hepatitis	12	9	75.0
Cerebrospinal meningitis	7	10	
Tuberculous meningitis	2	0	
Rheumatic fever	6	1	
Whooping cough	4	1	
Acute gastroenteritis	3	0	
Typhoid	2	1	

and the standard deviation 0.06. The upper limit of the thymol value for normal persons can be calculated as the mean values plus twice the standard deviation. The upper limit should thus be 0.20.

As appears from the curve, there is some divergence between the actual and the theoretic distribution as to the high values. By calculating the normal values as the mean plus twice the standard deviation, 5 per cent of the normal subjects are seen to present a pathologic condition. In the present series, however, 8 per cent fall outside the theoretic distribution curve. This is probably due to the fact that turbidity measurements generally are somewhat difficult, presumably because the flocculation does not occur uniformly each time. Moreover, a few normal persons must be expected to present pathologic values in consequence of past unnoticed infections.

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The series of patients comprised 373 persons suffering from different acute infectious diseases, as is seen in table 1.

Table 1 is based on 1,865 thymol analyses. Daily serial analyses were made on a number of the patients, especially those who had infectious mononucleosis, measles and mumps. In the patients with the other diseases, generally only a few analyses were made. Since establishment

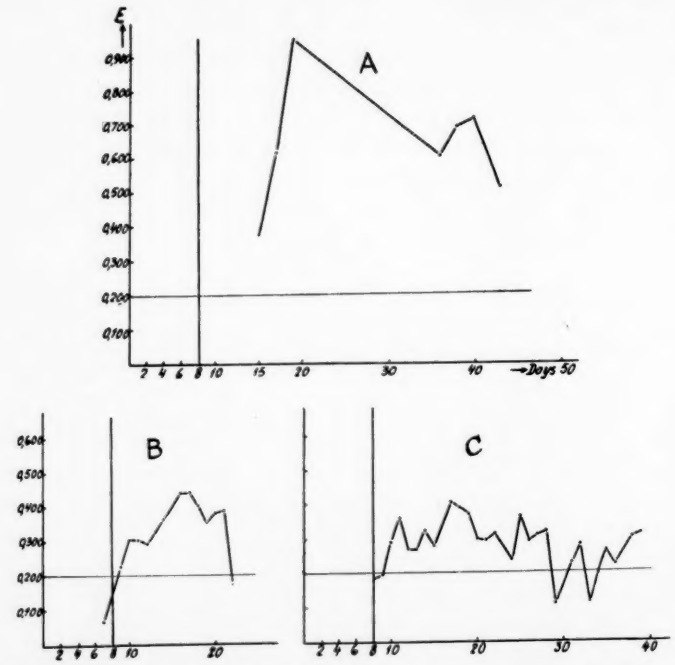

Fig. 2.—Results of the thymol turbidity test in patients suffering from measles. (Abscissa: days of illness; ordinate: the extinction value.) The vertical line indicates the time of cutaneous eruption; the horizontal line indicates the normal upper limit (extinction 0.20). *A*, results in a 1 year old girl. *B*, results in a 5 year old girl. *C*, results in a 4 year old girl.

of the upper normal limit is somewhat difficult, as is also the case in all other measurements of turbidity, a number of the normal results of thymol tests might be classed as presenting pathologic variations. This explains, no doubt, the few slightly positive reactions observed within the groups with mumps, scarlet fever and serous meningitis. The group with tonsillitis assumes an exceptional position in this respect, as will be discussed later.

The percentage calculation in table 1 is hardly an exact indication of the actual conditions; it must be somewhat arbitrary, because in some

cases only two analyses were made while in others numerous daily analyses were made.

A detailed description of the condition within each group follows.

Measles.—A total of 45 patients were examined, of whom 31 were observed daily over a rather long period, maximally fifty-six days. The day of appearance of the eruption was for practical reasons fixed at the eighth day of illness. Analysis of the patients before the appearance of the eruption was possible in a few cases only. In the majority of the cases (71 per cent) the reaction to the thymol test began to be evident at the onset of cutaneous eruption and remained positive for greatly varying periods. In a few cases the reaction became negative by the

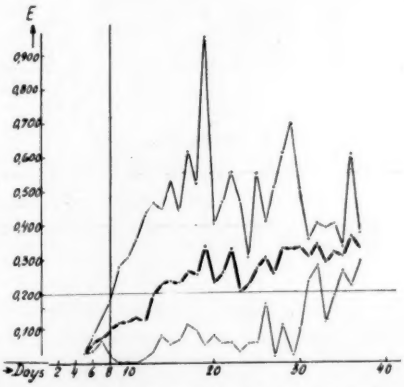

Fig. 3.—The average curve of reactions to the thymol turbidity test in 42 cases of measles (the thick line). The upper and lower curves (thin lines) indicate the maximal and minimal values of the reactions to the thymol turbidity test during each day of illness. (The vertical line, at the eighth day, indicates the time of the cutaneous eruption.)

twenty-second day. The present material does not allow any conclusions as to the maximum period of positive reactions.

Of the 45 patients, 71 per cent presented positive reactions at one time or other within the period of investigation. Four patients, kept under observation for some length of time, never presented positive reactions.

Figure 2 shows typical curves for 3 patients with measles. The vertical line indicates the day of appearance of the eruption. It is hardly due to chance that the curve of reaction to the thymol test begins to rise simultaneously with the appearance of the eruption. As, however, we do not know the pathogenesis of the eruption, this problem will not be gone into further. Figure 3 illustrates an average curve for all 45 cases. The maximal and minimal values for each day of illness have been plotted

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at the same time. The test is less pronounced than in the case of acute hepatitis, yet decidedly positive in by far the greater number of cases.

Some tests of hepatic function were made in all the cases in which the reactions were highly positive (Takata-Ara reaction, urobilin, urobilinogen and icterus index according to the method of Meulengracht). All these tests gave a negative reaction. In none of these cases was the reaction to the Paul-Bunnell test positive.

Perhaps the thymol turbidity test may be of practical importance for the differentiation between measles and conditions with morbilliform eruptions of different origin (e.g., eruptions due to drugs).

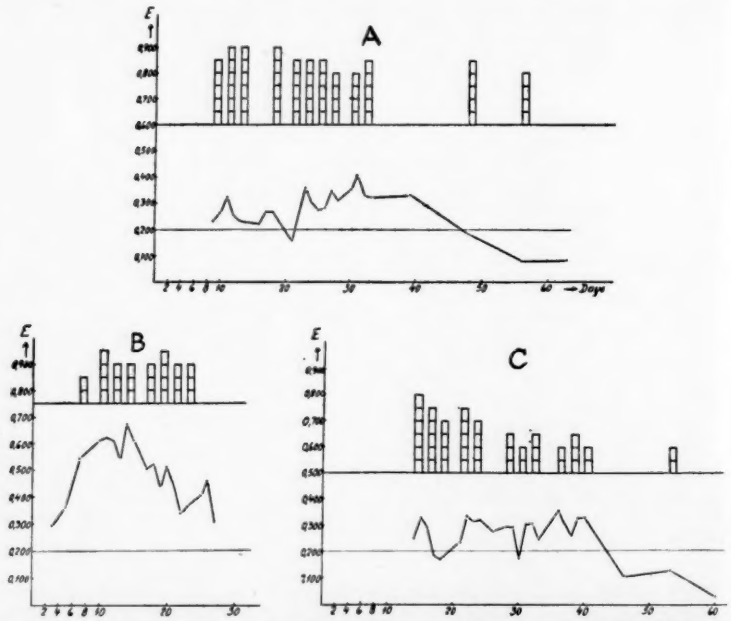

Fig. 4.—Results of the thymol turbidity test (curve) and the Paul-Bunnell test (columns) in patients with infectious mononucleosis. Each rectangle corresponds to agglutination in one tube. *A*, results in a 19 year old girl. *B*, results in an 8 year old boy. *C*, results in a 12 year old girl.

Infectious Mononucleosis.—A total of 34 patients were examined, of whom 29 were observed daily over a rather long period, maximally fifty-five days. The criteria applied for the diagnosis were as follows (Thomsen[15]): (1) tonsilitis, (2) multiple peripheral glandular enlargements and (3) mononuclear cells in the peripheral blood of over 4,000 per cubic centimeter.

15. Thomsen, S.: Studier over mononucleosis infectiosa paa basis af 549 tilfaelde, Thesis, Ejnar Munksgaards Forlag, 1942.

Since it is often difficult to fix the exact date of onset of infectious mononucleosis, the calculation of the days of illness is subject to some uncertainty. We calculated the days of illness from the day of onset of the tonsillitis. This is, however, somewhat arbitrary, because the patients had often been feeling ill for one to two weeks before the onset of the tonsillitis.

As a rule the reaction to the thymol turbidity test is positive when the patient is admitted to the hospital with tonsilitis, which most often

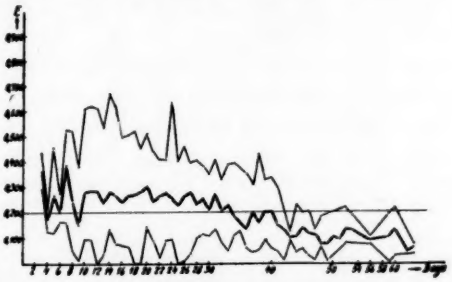

Fig. 5.—The average curve of the reactions to the thymol turbidity test in 33 cases of infectious mononucleosis (the thick line). The upper and lower curves (thin lines) indicate the maximal and minimal values of the reactions during every day of illness.

occurs one to two weeks after the actual onset of the disease. None of the present cases was, for this reason, observed from the beginning.

Figure 4 shows three typical curves for reactions to thymol turbidity tests in infectious mononucleosis. It appears that the reaction curve

Table 2.—*Reactions to the Thymol Turbidity Test and Paul-Bunnell Reactions in 34 Cases of Infectious Mononucleosis*

No. of Cases	Paul-Bunnell Reaction	Thymol Turbidity Reaction
20	Positive	Positive
6	Negative	Positive
7	Positive	Negative
1	Negative	Negative

may rise rather considerably. Figure 5 illustrates the course of an average curve for 33 patients, which shows that the reaction generally remains positive until the forty-second day.

A comparison was made between the reaction to the thymol test and Paul-Bunnell's reaction in all 34 cases of infectious mononucleosis. Paul-Bunnell's reaction was regarded as positive when there was agglutination in no less than four tubes.

It appears from table 2 that the reaction to the thymol turbidity test was positive in 26 cases of this not particularly large series, while the Paul-Bunnell reaction was positive in 27 cases. The reaction to both tests

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was negative in 1 case only. Thus, if both tests are used it seems that the diagnosis can be made with certainty in nearly all cases.

There is no convincing correlation in degree between the two reactions; neither is there any correlation as to the time, although they both most often are positive immediately at the patient's admission. Yet we have seen cases in which the thymol reaction became positive prior to Paul-Bunnell's reaction and vice versa (fig. 4).

Tests of hepatic function were made in all cases to the same extent as previously mentioned, and only 1 patient proved to have complicating hepatitis associated with jaundice.

Tonsillitis.—In dealing with the patients with tonsillitis we have distinguished between the following forms: (1) streptococcic tonsillitis, (2) nonstreptococcic tonsillitis and (3) tonsillitis in scarlet fever (table 1).

TABLE 3.—*Positive Thymol Reaction in Cases of Tonsillitis with Negative Paul-Bunnell Reaction (Presumably Cases of Infectious Mononucleosis)*

Case No.	Age of Patient (Yr.)	Duration of Illness Prior to Admission (Days)	Peripheral Glandular Enlargement	Streptococci in Throat	Thymol Turbidity Reaction	Results in Paul-Bunnell Test (Titer of Tubes with Agglutination)	Number of Mononuclear Cells	Comment
1	19	29	Present	Present	0.40	2	4,000	Presumably infectious mononucleosis
2	1	8	Present	Absent	0.85	0—2	10,050	Presumably infectious mononucleosis
3	2	2	Absent	Present	0.34	0—2	4,470	Probably not infectious mononucleosis
4	4	6	Absent	Absent	0.54	0—1	4,465	Probably not infectious mononucleosis
5	1½	?	Present	Absent	0.29	0	14,300	Presumably infectious mononucleosis
6	1	28	Absent	Absent	0.26	0—2	5,600	Presumably infectious mononucleosis

A total of 73 patients with scarlet fever were examined, two to four analyses being made in each case. The analyses were generally made between the third and the eighth day of illness. The reaction was observed to be positive in no more than 4 cases (5.5 per cent). As it was only slightly positive in these cases and as our normal series contained 8 per cent with supernormal values, we are justified in concluding that the reaction to the thymol turbidity test is not positive in scarlet fever.

Of the remaining patients with tonsilitis 82 were examined, among whom 9 showed a positive reaction to the thymol test. There was no difference in the frequency of positive thymol reactions between the cases with positive streptococcic observations and those with negative observations in the throat.

With this group, unlike the observations in the patients with scarlet fever, there were various patients with a highly positive reaction to the thymol test. A number of these patients were in all probability suffering from infectious mononucleosis, as will be shown.

After having reduced the number of cases of tonsillitis by these cases we found the incidence of positive thymol reactions within this group to be so small (6.1 per cent) that, as in scarlet fever, we could conclude that the thymol reaction does not become positive in tonsillitis.

The clinical data of 6 patients with tonsillitis with a highly positive reaction to the thymol test and a negative Paul-Bunnell reaction are illustrated in table 3. These cases, being of particular interest, will be analyzed further.

It appears from table 3 that the diagnosis in 4 out of the 6 cases might possibly be infectious mononucleosis. This diagnosis is supported by the long history before admission, which is typical for infectious mononucleosis, as well as the occurrence of peripheral adenitis and of increased amounts of mononuclear cells in the blood. It should be pointed out, however, that, of the 4 likely cases of infectious mononucleosis, in 1 peripheral adenitis was absent, while in 2 there was only moderate

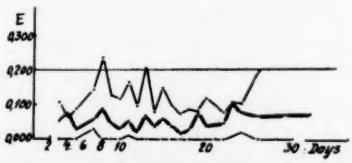

Fig. 6.—The average curve of the reactions to the thymol turbidity test in 25 cases of mumps (thick line). The upper and lower curves (thin lines) indicate the maximal and minimal values of the reactions during every day of illness.

monocytosis (i.e., less than 6,000 cells per cubic centimeter). Attention has been called to these cases, because we are of the opinion that the thymol reaction may contribute to the diagnosis in a greater number of cases of infectious mononucleosis, especially in children in whom the Paul-Bunnell reaction is often negative.

The practical importance of the facts stated here concerning the thymol test in tonsillitis and infectious mononucleosis lies in the possibility of distinguishing by means of this test between the two diseases on admission of patients.

Unfortunately, there were no cases of diphtheria among our patients in this period. It is therefore at present impossible to determine the significance of the thymol reaction for the important differential diagnosis of infectious mononucleosis and diphtheria.

Mumps.—A total of 31 patients were examined, most of whom had complications in the form of serous meningitis or orchitis. Ten were observed daily over a rather long period, maximally twenty-six days. Of the 31 patients only 2 (6.5 per cent) presented slightly positive reactions.

Figure 6 illustrates the average curve for all 31 cases, calculated for each day of illness. The maximal and minimal values for each day of

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illness have been plotted at the same time. The average curve is seen to be within the normal range.

Serous Meningitis (Cause Uncertain).—Thymol analyses were made in 47 cases of epidemic serous meningitis. The disease is most likely nonparalytic acute anterior poliomeylitis, but the disease may also be caused by another unknown virus.

The reactions in only 2 (4.3 per cent) of the 47 cases were observed to be slightly positive. Hence we feel justified in concluding that the thymol reaction is not positive in this disease.

Other Infectious Diseases.—A small number of thymol analyses were made for patients suffering from pneumonia, meningococcic meningitis, tuberculous meningitis, rheumatic fever, typhoid, erythema multiforme, smallpox, atypical exanthema, acute gastroenteritis and whooping cough. The reaction to the thymol test was observed to be positive in none of these patients, except in 1 of 2 patients with typhoid.

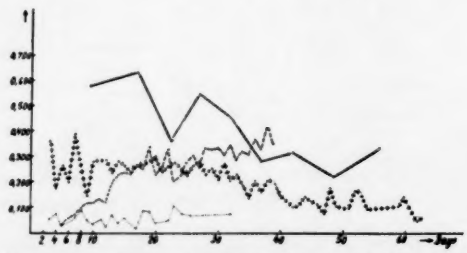

Fig. 7.—The average curves of the reactions to the thymol turbidity test in acute infectious hepatitis (continuous line), measles (broken line), infectious mononucleosis (crossed broken line) and mumps (dotted line).

Finally, a diagram is presented in which a quantitative comparison is made of the reaction to the thymol test in acute hepatitis, measles, infectious mononucleosis and mumps. The curves are average curves, mentioned in order of succession, according to the strength of the reactions (fig. 7).

COMMENT

The fact that a positive reaction to the thymol test is seen not only in hepatitis but also in measles shows that a positive reaction is not exclusively a criterion of hepatic damage. It is well known that hepatitis never occurs in association with measles, and the tests of hepatic function never revealed signs of hepatic damage in our patients, although we observed even very high thymol values in a number of our patients with measles.

In infectious mononucleosis the positive thymol reaction indicates nothing certain, even though we found only 1 case of manifest hepatitis

and never other signs of hepatic damage with the tests of hepatic function used. Cohn and Lidman[16] recently described 15 patients with infectious mononucleosis without jaundice, all of whom presented a positive thymol reaction as well as signs of hepatic damage according to the reaction to the sulfobromophthalein sodium test.

It is therefore logical to assume that the thymol reaction in measles, infectious mononucleosis and hepatitis indicates certain changes in the serum globulins. This may be directly connected with the antibody production. Nothing can be said as to whether these changes in the serum globulins are of a qualitative or a quantitative nature.

The curves for measles and infectious mononucleosis show that the thymol curve bears a certain resemblance to that for the antibody concentration in infectious diseases.

Our investigations were started to determine whether the thymol reaction is positive in the virus infections in which here the gamma globulin has proved to have a curative or protective effect. The fact that the reaction to the thymol test proved to be positive in measles and negative in mumps seems to be against the hypothesis that the thymol reaction alone may be an indicator of a change in the gamma globulins.

On the other hand, the observation that in three widely different virus diseases a positive reaction to the thymol test can occur might tempt one to conclude that the reaction indicates the effect of a common antigen in the three virus forms. This conclusion is, however, hardly justifiable on the basis of the present investigations.

By way of summing up, we may say that the thymol test is hardly a test of hepatic function, but is rather to be regarded as an indicator of changes in the serum proteins in consequence of different virus infections.

SUMMARY

An investigation has been made employing MacLagan's thymol turbidity test of 373 patients suffering from different acute infectious diseases. The normal upper limit has been calculated as the mean value of 0.08 extinction plus twice the standard deviation, equal to 0.20 extinction.

The reaction to the thymol turbidity test was observed to be positive in measles (71 per cent), infectious mononucleosis (73.5 per cent) and acute infectious hepatitis (75 per cent), whereas it was negative in tonsillitis, scarlet fever, mumps, serous meningitis, pneumonia, purulent meningitis, tuberculous meningitis and acute gastroenteritis.

In measles the reaction becomes positive with the appearance of the eruption and remains positive for several weeks. The thymol test pos-

16. Cohn, C., and Lidman, B. I.: Clin. Investigation **25**:145, 1946.

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sibly is of practical importanc for the differential diagnosis of measles and other kinds of morbilliform eruptions.

In infectious mononucleosis the reaction to the thymol test is generally positive at the time of the patient's admission and remains so for an average of six weeks. The thymol test may be employed as a supplement to the Paul-Bunnell test, since with both tests a positive reaction can be obtained in nearly all cases of infectious mononucleosis.

Since the tests employed by us revealed no signs of hepatic damage in association with infectious mononucleosis and measles, the thymol test must probably be regarded as a means of indicating changes in the serum proteins in consequence of the virus infections rather than as a proper test of hepatic function.

ADRENAL CORTEX AND ARTERIAL HYPERTENSION

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A. INTRODUCTION

Increased arterial blood pressure of known or suspected origin is an extremely common sign, listed in association with at least fifty-two diseases. Thus it is present in certain rare disorders of the endocrine glands, such as tumors of the adrenal glands or of the anterior pituitary gland (basophil adenoma). In cases of renal insufficiency there is a considerably elevated blood pressure. However, the fact remains that patients with these disorders constitute hardly more than 3 to 5 per cent of those with hypertension.

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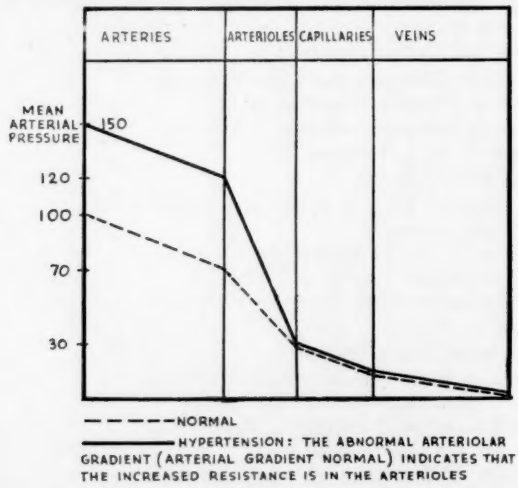
Hypertensive vascular disease ("essential hypertension," Frank, 1911; hyperpiesia, Clifford Allbutt, 1895), including the malignant variety (Keith, Wagener and Kernohan, 1928) is far more commonly encountered than is high blood pressure due to all other causes and is now the leading cause of death, by far outstripping even cancer. Over 100,000 persons die every year in England and Wales from the effects of hypertension. Its origin and cure have been one of the persistent problems confronting physicians. Little is known about the underlying cause of this condition, though much has been learned about this type in the last few years. The employment of the word "essential" has been used to indicate ignorance of the cause of the condition.



Illustrating the site of increased vascular resistance in hypertension.

Ideas concerning the etiology and the nature of chronic hypertension have been for the most part based on experimental work on animals and on clinical observations on human beings. There is good reason to believe that arterial hypertension is due to increased vascular resistance which is the result of widespread narrowing of the arterioles in the peripheral circulation and, to a slight degree or secondarily, in the pulmonary circulation and the right ventricle (Page and Corcoran, 1945).

In the majority of cases renal excretory function is not seriously impaired and the kidneys show little gross alteration in structure, though other renal functions of "hormonal" nature may be abnormal. Excretory and pressor-endocrine functions of the kidney are independent. After the arteriolar vasospasm has persisted for years, a diffuse hyperplastic vascular sclerosis (hypertensive vascular disease) results, which

is eventually responsible for failure of such organs as the heart, brain and kidneys.

Among the causes of the disease that have been advanced are (*a*) a primary disturbance in the vascular system, (*b*) abnormal endocrine secretion, (*c*) abnormal sympathetic discharge from the higher autonomic (hypothalamic) centers, or (*d*) the liberation of excessive amounts of a pressor substance produced by the renal epithelial tissue.

One important fact realized in the field of hypertension is that hyperactivity of the nervous system is not the primary cause of arterial hypertension, although some do believe it may play a part. There is no evidence that the sympathetic system is important in the causation of hypertensive vascular disease. The operation of double thoracolumbar sympathectomy now in vogue must be regarded as a nonspecific symptomatic treatment of the disease (Gold, 1945). There is no doubt that the autonomic nervous system, with the central autonomic nuclei, plays a part in maintaining arterial blood pressure and in elevating or depressing it. It is possible that this neurogenic element is a factor in the early phase of hypertension, but it is reenforced or replaced later by a humoral mechanism. Most research has supported the view that a chemical substance liberated by the kidneys elevates the blood pressure, but there is a growing body of acceptable evidence against the concept of a primary renal "ischemic" origin of human hypertensive vascular disease.

The nervous system undoubtedly mediates in the demands of the body for quick changes in the distribution of the blood, but the slow changes are caused by humoral agents.

According to investigations in recent years, it is believed, as stated previously, that arterial hypertension is the result of narrowing of the arterioles (precapillary arteries) in major vascular fields. It is not due to changes in the blood volume, or to increased viscosity of the blood, and while powerful left ventricular contractions are necessary for its maintenance, they are not causal. The constriction of the peripheral vessels may ultimately result from various humoral mechanisms; "pressor" substances at present incompletely identified may circulate in the blood, cause narrowing of the arterioles and thus increase the blood pressure.

Experimental work performed in recent years has demonstrated that the adrenal cortex plays a role in the pathogenesis of hypertension. Certain of the more important aspects of this problem are reviewed here.

Some features of the anatomy and physiology of the adrenal glands will be described first to aid in the understanding of their function and of their relationship to other systems of the body.

The adrenal (suprarenal) glands are two small masses which in man lie at the upper poles of the kidneys. They attain their greatest weight,

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about 6 Gm. each, between the ages of 16 and 30 years. The glandular cortical portion is vital to the organism.

The cortex and the medulla are of distinctly different developmental origin and in effect have been regarded as two endocrine organs. The adrenal cortex, which is of mesodermal origin, develops from the wolffian ridge in common with the ovaries and the testes and is related embryologically to the cortex of the kidney. Accessory adrenal bodies, or adrenal "rests," consisting of cortical substance, are commonly present in the liver and other structures, e.g., Marchand's organ in the broad ligament near the ovary, which is almost constantly present.

The functions of the cortex and the medulla may be influenced by their intimate vascular relationships. The vascularity of the adrenal glands is such that more blood passes through them than any other organ with the possible exception of the thyroid. Senescent changes are found in the arterioles to these glands as in other organs in normotensive subjects. In hypertension the changes in the adrenal arteries rank third in frequency, after those in the spleen and kidneys (Page and Corcoran, 1945). These vascular changes may be of importance in view of certain recent work (Victor, 1945) to be described later. A significant feature of the adrenal veins is the longitudinal bundles of muscle, contraction of which can apparently block the blood flow from both medulla and cortex, thus regulating adrenal secretion. This phenomenon is not yet properly understood. The recent work of Trueta and others (1946) in diverting the renal blood flow from the renal cortex by appropriate stimulation of the nerves suggests further the importance of the study of the adrenal blood flow.

The adrenal cortex is stated to be abundantly supplied with nerve fibers, but little is known regarding the effect of nervous influences on this portion of the gland. Myelinated fibers are stated to be abundant in the nerves distributed to the capsule and the cortex, while none is said to occur in the medulla, which is richly supplied with unmyelinated fibers. Nerves in a cortical plexus are described as giving rise to networks about the cortical cell groups, and many fibers terminate in relation to cortical cells. Denervation is not believed to abolish cortical function.

Bennett (1940) has presented evidence that (in the cat) there is no innervation of the adrenal cortex, and he has pointed out that what others have called an extensive and intricate network of fine nerve fibers resemble closely the impregnated argyrophile connective tissue collagen fibers in his sections.

The adrenal cortex, like so many other endocrine glands, is under the influence of factors elaborated by the anterior pituitary gland. Regarding the relationship between these two glands and the blood pres-

sure, more detail will be given later in this work, but the following points may be mentioned here. After hypophysectomy in rats, the blood pressure falls rapidly in eight days, but the injection of desoxycorticosterone or of adrenocorticotrophic hormone raises the level almost to normal. The subnormal blood pressure in the hypophysectomized rat is therefore mostly due to the resultant insufficiency of adrenal cortex (Braun-Menendez, 1944). Hypophysectomy also causes a fall of the blood pressure of rats with "renal" hypertension, which can be restored to the original level by the use of purified adrenocorticotrophic hormone (Anderson, 1944).

The investigations of Selye over many years, described in a review article recently written by him (1946), suggest that some of the most important diseases of man, such as hypertension, nephrosclerosis and the rheumatic disorders, may result from endocrine reactions which occur with long-continued exposure of the body to stress. Various noxious agents elicit pathologic and biochemical changes in the organism which are always the same irrespective of the stimulus. The sum of these nonspecific adaptive reactions is called by him the "general adaptive syndrome." During this syndrome, certain hormones of the anterior pituitary gland and the adrenal cortex are produced in excessive amounts as a defensive endocrine response, and these may become the cause of certain cardiovascular, renal and joint disorders, i.e., diseases of adaptation. These views of Selye will again be referred to; they have received widespread pubication and consideration.

The role of the adrenal glands in the production of hypertension is thus by no means limited to the discharge of epinephrine. The significance of the cortex, pointed out long ago by Josue and Pilliet, is beginning to receive more attention.

Loss of function of the adrenal cortex, usually through tuberculosis or atrophy, results in Addison's disease, one striking feature of which is hypotension. No clinical condition has been attributed to overproduction of cortin, expect with regard to the hormones responsible for some of the features in Cushing's syndrome (Albright, 1942) and the adrenocortical syndrome.

The association of hypertension with adrenocortical tumors is well established. One of the striking features of functioning "tumors" of the adrenal cortex is the variety and variability of the clinical pictures which they produce. The manifestations of hyperfunction vary remarkably from case to case; age, sex, mode of onset and quantitative and qualitative differences in hormone output determine the varied symptomatology and the termination of the disease. The differences in the clinical manifestations are not surprising, since the adrenal cortex is known from chemical studies to contain many factors, while clinical and experimental

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evidence indicates that the cortex has several functions which in turn may not be related. Certain tumors give rise to pathologic masculinization due presumably to the production of androgenic substances. The cortex is important in metabolism and in the maintenance of sodium and potassium balance, the plasma volume and the blood pressure. It is important in the maintenance of the blood pressure in a case of hypertension, as it is in the animal with a normal blood pressure. Whether it is involved in "renal" hypertension in any other sense still awaits final proof. The relationship of adrenal cortex function to renal cortex function in the regulation of normal blood pressure and in hypertension will be considered in more detail later.

Nodular hyperplasia and excessive lipidosis of the adrenal cortex with or without medullary hyperplasia are frequently associated with hypertension. In man spontaneous tumors or hyperplasia of the adrenal cortex cells secreting desoxycorticosterone (or desoxycorticosterone-like substance) or corticosterone has not been recorded. These may exist. The adrenal glands are remarkably stimulated by exposure to diverse noxious agents. Selye (1936, 1946) has attempted to show how this stimulation affects the production of the salt-regulating or carbohydrate-regulating factor or influences some other unknown functions.

Certain qualitative and quantitative chemical and biologic procedures developed in recent years have made it possible to assess functions of the adrenal cortex not only in animals but in man.

In spite of many investigations on the function of the adrenal cortex, the intimate mechanisms underlying its activity remain obscure. Two ways of studying the function of such an endocrine gland, apart from such procedures as adrenalectomy, are (1) to determine the effect of its hormone on biologic processes and (2) to determine the conditions which affect the formation and liberation of its specific hormones, using a direct or indirect approach.

Thus direct determinations can be made of alterations of the hormone or its known metabolites in the gland itself, in the blood stream or in the urine. Indirectly, determinations can be made of the metabolic changes characteristic of the action of the hormone. Regarding hormone in the gland, estimations have not proved feasible owing to the low content of hormone in the gland at any one time. The level of the hormone in the blood has been studied by Vogt (1943 to 1945) and will be referred to again later. Urinary excretion products that may be estimated are as follows:

1. 17-ketosteroids. These are not entirely an indicator of adrenal cortical hormone secretion.

2. "Cortical-like material" (urinary cortin). Weil and Browne (1939), Venning and Browne (1944) and Dorfman and his colleagues

(1942 to 1946) have shown by assay in rats that a variety of stresses increase the excretion of these hormones. Lowenstein, Corcoran and Page (1946) recently described a chemical method for determining corticosteroids (both active and partially reduced).

Alterations in the cholesterol and ascorbic acid contents of the adrenal cortex appear to be associated with secretory activity of the gland. These substances appear to be directly associated with the formation of cortical hormone (Long, 1946), cholesterol being the reserve steroid material from which the hormone is formed, to be excreted with ascorbic acid. A wide variety of stresses, endogenous and exogenous,for example, cold, hemorrhage, burns, infections, drugs, may activate the adrenal cortex to secrete its hormone, as emphasized by Selye. There is a fall in the cholesterol and ascorbic acid contents of the gland. This response is believed to be produced through the anterior pituitary adrenocorticotrophic hormone.

More detailed information on the morphologic, experimental and clinical investigations of the adrenal cortex will be discussed under appropriate headings in subsequent sections of this work in an attempt to show that abnormal function of this endocrine gland appears to be significant in the production and maintenance of hypertension.

B. RENAL HYPERTENSION, WITH SPECIAL REFERENCE TO THE ROLE OF THE ADRENAL CORTEX IN THE "RENAL PRESSOR SYSTEM."

Experimental Observations in Animals.—Progress in the clinical investigation of hypertension has been made in recent years since it became possible to "reproduce" the disease in animals by constriction of the renal arteries or by compression of the renal parenchyma.

In his classic experiments started in 1928 Goldblatt (1937) demonstrated that hypertension of great severity and of prolonged duration could be produced in the dog without loss of urea clearance by constriction of one or both renal arteries. Adequate constriction of both main renal arteries either at the same time or at an interval caused persistent hypertension which lasted for years. Similar results have been obtained by partial occlusion of the aorta just above the origin of the renal vessels. Both the systolic and the diastolic pressure became elevated, in proportion, much as in human nephritis (Wood and Cash, 1936). Hypertension has been produced by the same method in other animals, for example, the monkey, goat, sheep, rabbit and rat, while recently Quinby and others (1945) have demonstrated that by constriction of the renal artery in man the renal humoral pressor mechanism is stimulated to activity as it is in animals. Page (1939) has produced similar hypertensive effects in animals by wrapping the kidney in cellophane or

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silk; the resulting aseptic perinephritis produces a fibrocollagenous hull around the parenchyma. This apparently causes hemodynamic alterations in the kidney which lead to the development of hypertension.

The experimental work of many investigators has suggested that the development of arterial hypertension associated with "renal ischemia" is due to a humoral mechanism in the kidney which is not dependent on the nervous system (the whole sympathetic system can be removed, yet the hypertension persists) or on the endocrine system with the possible exception of the adrenal cortex, which was considered at the least to be important in determining the degree of response.

Trueta and his collaborators (1946) have recently published interesting and important findings the implication of which may be far reaching. They have shown that in the experimental animal appropriate stimulation of the nerves may divert the renal blood flow from its commonly accepted course and that as a result the renal cortex may be partly or completely deprived of its supply, the blood being short-circuited through the medullary channels. Thus the suggestion has been made that hypertension may arise from abnormal activity of nerve centers from which impulses effect cortical ischemia and medullary congestion.

The production of experimental hypertension by compression of the renal artery is impossible in adrenalectomized dogs, and adrenalectomy is followed by a prompt fall in the blood pressure of dogs previously made hypertensive by clamping of the renal arteries. Goldblatt found that bilateral adrenalectomy abolishes the experimental renal hypertension and that the hypertension can be produced if even a minute portion of adrenal cortex is left or if the completely adrenalectomized animal is given cortical extract. Sustained hypertension can be produced even after the removal of one adrenal completely and the destruction of the medulla of the second, which indicates the importance of the cortical rather than the medullary portion in this connection. Blalock and Levy (1937), Page (1938) and Grollman (1940) also showed that the complete syndrome of experimental hypertension does not occur in the adrenalectomized animal. Dell'Oro (1942) reported that adrenalectomy produces an abrupt and marked decrease in the blood pressure of hypertensive rats, which can be only partially corrected by administration of desoxycorticosterone. Certain workers, however, were not able to confirm these results. Thus, Taquini (1938) found that implantation of an ischemic kidney in a dog with its adrenals removed causes permanent hypertension, and Rogoff and others (1939) concluded that neither cortex nor medulla plays a significant role in the causation of "renal" hypertension. Since so many independent investigators have found the contrary in large numbers of experiments, it is important that these workers point out where their experiments differ from those of the others.

Two explanations for the disturbance of hemodynamics produced in the kidney by the procedures mentioned have been (*a*) that the kidney is rendered "ischemic" (Goldblatt) or (*b*) that its blood supply is changed from a pulsatile to a continuous flow (Page). The latter view is the one now accepted. The disturbed circulation causes the liberation by the epithelium of the proximal convoluted tubules (and probably not by the cells of the juxtaglomerular apparatus of Goormaghtigh, as has been suggested by some authors) of a protein called renin. This acts in the blood stream on a renin substrate (α 2-globulin) called preangiotonin or hypertensinogen to form a pressor substance called angiotonin (Page and Helmer) or hypertensin (Braun-Menendez and his associates). The latter substance has been shown to have a vasoconstrictor action. It is gradually inactivated by blood and tissue enzymes called angiotoninase or hypertensinase, the level of hypertensin in the blood plasma depending on the relative velocity of its production and destruction (Cruz-Coke and others, 1945).

$$\text{Renin+Hypertensinogen} \xrightarrow[\text{reaction}]{\text{Anaerobic}} \text{Hypertensin}$$

$$\text{Hypertensin+"enzyme"} \begin{cases} \text{protease} \xrightarrow[\text{reaction}]{\text{Anaerobic}} \text{amino acids} \\ \text{oxidase} \xrightarrow[\text{reaction}]{\text{Aerobic}} \text{X} \end{cases}$$

The renin substrate hypertensinogen is a globulin formed in the liver and possibly in the adrenal cortex. It decreases and even disappears from the systemic blood of untreated adrenalectomized male dogs (Lewis and Goldblatt, 1942; Houssay and Dexter, 1942). Adequate therapy with adrenal cortical hormone or with desoxycorticosterone results in a return of the level of hypertensinogen to normal. However, before attributing to the adrenal cortex an influence in the formation of hypertensinogen, the possibility should be eliminated that the low blood pressure of untreated adrenalectomized dogs, through liberation of renin by the kidney (Huidobro and Braun-Menendez, 1942), is not the cause of the disappearance of hypertensinogen from the blood.

Bilateral adrenalectomy and other procedures are reported to cause no change in the sensitivity of dogs to the pressor action of hypertensin (Houssay and Dexter, 1942). Several workers have shown that bilateral adrenalectomy decreases the response to injections of renin (Page, 1939; Williams and others, 1939; Friedman and his associates, 1940; Remington and others, 1941; Swingle and Remington, 1944). Bilateral adrenalectomy also prevents the appearance of a substance like angiotonin in the blood when experimental hypertension is produced in the dog by injection of kaolin into the cerebral ventricles.

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Recently, Gaudino (1945) concluded from his experiments on rats that the presence of adrenal cortex tissue or of one or more of its hormones (desoxycorticosterone or 17-hydroxy-11 dehydrocorticosterone) seems necessary for the existence of renal hypertension and for the maintenance of normal arterial pressure. Thus in hypertensive adrenalectomized rats, administration of desoxycorticosterone and especially of 17-hydroxy-11-dehydrocorticosterone reestablished hypertension; cortical extracts (in the doses used) produced little or no effect.

Goormaghtigh has described a granular reaction and an increase in the number of the afibrillary cells in the kidney in long-continued hypertension caused by interference with the renal circulation. Removal of the kidney did not abolish the hypertension; it was suggested that an extrarenal factor is responsible for the raised pressure (editorial, *Lancet* **2**:747, 1945).

Kottke and others (1945) were able to produce severe long-standing hypertension in dogs by appropriate renal artery-nerve stimulation, which persisted as long as the stimulation was maintained; however, as elevation of the blood pressure was not observed in anesthetized animals, they inferred that the hypertension is not due to the simple hemodynamic effects of renal vascular constriction.

Pickering (1945) concluded that during the first week after constriction of the renal artery in the rabbit hypertension is due solely or chiefly to the release of a humoral agent, probably renin, from the "ischemic kidney." Later a new and nonrenal factor plays an important and perhaps the chief role in maintaining the raised pressure.

The adrenal cortex is controlled by the anterior pituitary gland. Rats made hypertensive by partial ligation of one renal artery were hypophysectomized completely; this caused a fall of the blood pressure but not to a normal level except in those animals in which the hypertension had been present less than one month. A purified adrenocorticotrophic hormone preparation restored the renal hypertension to the level present before hypophysectomy.

After the production of experimental renal hypertension in rats, hypophysectomy or adrenalectomy causes a fall of blood pressure, in some cases to below normal. The hypertension may then be partially, though rarely completely, restored by administration of desoxycorticosterone or of adrenal cortex extracts. Steroids such as progesterone, testosterone or estradiol did not raise the blood pressure in such animals in the experiments of Page and others (1946).

The failure to prevent completely the drop in systolic blood pressure following hypophysectomy in normal rats or in adrenalectomized hypertensive rats by replacement therapy with adrenal cortex extract or desoxycorticosterone suggests that either (*a*) the dosage or method of

administration has been inadequate or (*b*) there is some factor other than desoxycorticosterone elaborated by the adrenal cortex that exerts an influence on the blood pressure.

All the work so far described, which started with the first report by Goldblatt of a method by which experimental hypertension can be produced in animals by the application of suitable clamps to the renal vessels or the aorta, must now be viewed in the light of a recent report by Victor (1945). In experiments on dogs it was found that ligation of the vessels to one adrenal gland (the left) leads to a prompt rise of blood pressure from an average of 125 mm. of mercury to levels of 225 mm. or more. This hypertension was sustained for several months up to the time of publication (March 1946) and is comparable with that produced by the Goldblatt method of constriction of the renal arteries. Ogden and others (1948) have repeated and confirmed this work.

Observations in Man Regarding the Renal-Pressor System.—Morphologic evidence that hypertension is not necessarily secondary to renal disease was furnished by Castleman and Smithwick (1943). They investigated biopsy material obtained from the kidneys during operations for subtotal sympathectomy in hypertensive patients and discovered a considerable number of normal kidneys both on gross inspection and on microscopic examination. Master and others (1943) also carried out renal biopsies in the course of splanchnic resections in 100 patients with hypertension. They concluded that in more than half the cases morphologic evidence of renal vascular disease was inadequate as the sole factor producing the hypertension and that in many cases hypertension preceded the renal vascular lesion. They thought that their observations were not in keeping with the conception that renal ischemia is the cause of hypertension in man. Hypertension, although present more often than not in patients with intercapillary glomerulosclerosis, is not a necessary part of the clinical picture; when present, it is in all probability associated with the arterial nephrosclerosis which is commonly present in diabetes mellitus.

Goldring and others (1941) found no evidence in their investigation of 60 hypertensive patients to warrant the contention that renal ischemia is the primary cause of hypertension. Friedman and others (1941), reporting a parallel study, stated that it appears highly probable that renal ischemia, although present in the majority of their hypertensive patients, may well be a secondary or concomitant mechanism in the pathogenesis of essential hypertension. Thus the renal ischemia found in the hypertensive patient may be only a local manifestation of a generalized vasoconstriction, sharing in the latter and possibly aggravating it but not primarily causing it.

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The efforts of Homer Smith (1943), through his own experiments and the work of others involving methods devised by him, proved that in many cases of hypertension not only is renal function normal but the flow of blood through the kidneys is not diminished.

The hypertensinogen concentration of the plasma was found to be normal in patients with hypertension and in a case of Addison's disease but often significantly decreased in cases of hepatic insufficiency (Haynes and Dexter, 1943). Normal concentrations of hypertensinase have also been found in the plasma of patients with hypertension.

Page (1940) demonstrated an excess of angiotonin-like vasoconstricting substance in the blood of patients suffering from "essential" hypertension and from "malignant" hypertension (rapidly progressing hypertensive vascular disease).

Gregory and others (1944) presented evidence to show that angiotonin is not involved in the pathogenesis of "essential hypertension," and Browne (1944) also stated the belief that this substance is not responsible for the hypertension of eclamptic toxemia. Grimson, too, concluded that there is no incontestable evidence that the renal hypertensive mechanism initiates the so-called essential hypertension in man (1942).

An important investigation because of its direct approach is that of Dexter and Haynes (1944), who measured the amount of renin in the blood of various types of patients with increased blood pressure. They found renin only when the blood pressure was rising acutely (1 case of eclampsia, 2 of severe preeclampsia and 1 of fulminating acute glomerulonephritis were studied). None was found in cases of mild toxemia of pregnancy, moderate acute glomerulonephritis and chronic hypertensive vascular disease of all degrees of severity. They suggested that the renin pressor system may be involved only initially in the development of hypertension.

Quinby and others (1945) have demonstrated that constriction of the renal artery stimulates a humoral pressor mechanism to activity in man as it does in animals.

The view that a "renal" factor is the cause of hypertension has been less favored as the evidence for it has become more complex.

The properties of renin suggest that it is normally concerned with the regulation rather than the maintenance of normal blood pressure, and the development of tachyphylaxis gives cause for doubt as to whether excess of renin can be responsible for a persistently elevated blood pressure.

The Hypertensive Toxemias of Pregnancy (Preeclampsia and Eclampsia).—The frequency with which hypertension coexists with pregnancy has received increasing attention in recent years.

Two common conditions are (*a*) pregnancy occurring in a patient with essential hypertension and (*b*) pregnancy "toxemia" occurring in a healthy woman and leading to preeclampsia and eclampsia.

Since the work of Goldblatt was published, the latter conditions have come to be regarded by many as the same as that which is known in the nonpregnant state as "essential hypertension." Against this is the fact that eclampsia never occurs with hypertension except in pregnancy. Tillman (1942) suggested that it represents the disease as it occurs in the nonpregnant subject plus additional disease directly due to the pregnancy, i.e., that hypertension predisposes to the occurrence of toxemia during pregnancy. However, Page (1938) transfused 400 cc. of blood from each of several patients suffering from either eclampsia or preeclampsia into normal pregnant women, without causing a significant rise of blood pressure in any case. That a humoral factor is concerned is shown by the fact that the vasospastic phenomena and the increased blood pressure are often reduced by the termination of pregnancy.

Fishberg has written that in a small proportion of the cases the condition develops in women with an endocrine disturbance which resembles Cushing's syndrome in the nonpregnant state. The women in these cases present obesity of girdle distribution, a pudgy face, stocky build and more or less hypertrichosis of male distribution, the pelvis being predominantly anthropoid rather than gynecoid (Fishberg, 1939). According to Williams and Harrison (1939), also, perhaps 10 per cent of cases of so-called essential hyptertension present the features of the basophilic syndrome in some degree.

By inducing experimental "renal ischemia" in pregnant dogs and rabbits, Dill and Erickson (1939) produced a picture closely resembling that in human eclampsia. They concluded that some factor other than simple renal insufficiency must be concerned in the rapid and fatal course noted in the pregnant animals.

As is true of hypertensive vascular disease in general, little is known about the pathogenesis of the acute hypertensive syndrome of pregnancy, and theories are legion.

Browne (1944) considered that the hypertension of eclamptic toxemia cannot be due to the renin-hypertensin mechanism or to a primary renal ischemia from any cause whatever. He stated the belief that the pressor mechanism in toxemia is a humoral and not a nervous one but that the pressor substance is not angiotonin (hypertensin), tyramine or epinephrine. Dexter and Haynes (1944), who found renin in the blood in 1 case of eclampsia, 2 of severe preeclampsia and 1 of fulminating acute glomerulonephritis, suggested that the renin-pressor system may be involved only initially in the development of hypertension.

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In a more recent communication, Barnes and Browne (1945) considered toxemia of pregnancy a temporary disorder leaving no permanent lesion. They stated that preeclampsia and true eclampsia do not cause permanent vascular or renal damage. Not all obstetricians agree with these views (Greenhill, 1945).

Little research has been done on any possible relation between adrenal disorders and the toxemias of pregnancy. In a search for the causes of edema and hypertension in eclampsia, the adrenal cortex deserves attention. It has been deduced that the decidual cells of the maternal placenta may liberate a factor causing maternal hypertension by chemical means (Sapeika, 1943) in a humoral mechanism in which the adrenal cortex might play a part. Parks (1943) suggested that in the last trimester of pregnancy the extra cortical secretion from the fetal adrenal glands might cause a disturbance in electrolyte distribution. There is not at present any suitable method of measuring the excretion of metabolites derived from adrenal substances which regulate water and electrolyte metabolism. The maternal rather than the fetal adrenal glands would appear to be the possible offender (Venning, 1946). Smith and Smith (1945) concluded that preeclampsia and eclampsia are related to premature deficiency of the placental steroid hormones; this, they stated, results in the elaboration of a toxic substance, presumably in the decidua, which accounts for the eclamptic syndrome.

It has been claimed that the signs and symptoms of toxemia of late pregnancy are due to the retention of sodium chloride in excess in the extracellular tissues, with dehydration of the cells. The sodium ion is detrimental in pregnancy when sodium chloride and sodium bicarbonate are given in excessive amount. The injection of hypertonic sodium chloride solution in a nontoxemic pregnant woman has produced an eclamptic syndrome (editorial note in the "1945 Year Book of Obstetrics and Gynecology").

C. CHANGES IN THE ADRENAL CORTEX ASSOCIATED WITH HYPERTENSION IN MAN

The relation of the endocrine system to the level of arterial pressure is known to the clinician from his knowledge of hypotension in Addison's disease and of hypertension in Cushing's syndrome and in certain adrenal carcinomas.

The role of the adrenal cortex in the production or maintenance of hypertension has not been fully elucidated, but the possibility of its importance is suggested by the experimental work mentioned in the previous sections and by certain well known clinical and pathologic observations which are described in the following paragraphs.

Autopsy Studies.—There is considerable anatomic evidence that hyperplasia or adenomatous change of the adrenal cortex is a frequent concomitant of arterial hypertension, the incidence of such morphologic change being greater than could be accounted for by the factor of age alone. The pathologic hypertrophy of the cortex may be diffuse or nodular in type. In adults, cortical hyperplasia occurs mostly as nodules, which are small, not exceeding the size of a pea. Such nodular hyperplasia is observed at autopsy in a variety of hypertensive conditions, especially in nephritis and atherosclerosis. In other hypertensive patients, however, there may be no evidence of cortical hyperplasia, the size of the adrenals being within normal range; adenomatous hyperplasia also occurs in the absence of hypertension.

Morphologic evidence suggests that the adrenals share some measure of responsibility for hypertension. Sarason (1943), in a study of the adrenal glands, found cortical enlargement, with an increased amount of lipid, in cases of hypertension; the change was more striking when the hypertension was associated with primary vascular disease and less striking when chronic glomerulonephritis or pyelonephritis was a feature. No explanation is available for these changes. No significant alterations were present in the series of cases of atherosclerosis. Philpot (1909) found the mean weight of the adrenals to be much greater in those who had "chronic nephritis" than in comparable patients of the same age group without hypertension.

Rinehart and his associates (1941) reported that adenomatous hyperplasia of the adrenal cortex was almost regularly found in association with hypertensive vascular disease. They described nodular hyperplasia as pathognomonic of the disease, based on the comparison of the adrenal glands in 26 hypertensive and 100 control subjects, and they claimed that hyperplasia of the cortex in hypertensive vascular disease is almost as definite as that of the thyroid in exophthalmic goiter. The mean combined weight of the adrenals was greater by 4.2 Gm. in a group of patients with hypertensive vascular disease than in a control group. Hyperplasia was also noticed in 8 out of 9 cases of chronic pyelonephritis.

Dempsey (1942) was unable to confirm these findings, maintaining that hypertensive subjects have no greater incidence of histologic alteration in the adrenal cortex than subjects with normal blood pressure. His arguments would, however, carry more weight if they were based on a larger amount of material. Dublin (1943) also could find no constant relationship between structure and function of the adrenal cortex in the pathogenesis of hypertension. In the course of studies on excretion of 17-ketosteroids, Bruger and others (1944) could find no difference in the incidence of hyperplastic or adenomatous changes in the adrenal cortex of hypertensive and normotensive subjects. There are reports that

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the size of the adrenal gland is not altered by a preexistent hypertensive state (Dempsey, 1942; Koehler, 1936).

In the most recent and most comprehensive series of cases reported, Russi and others (1945) found the incidence of benign adenomas of the adrenal cortex in 9,000 routine autopsies to be at least 1.45 per cent. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general group, and both diseases were frequently present in association with such a tumor. In relation to hypertension, the authors stated the belief that there is a direct effect of the cortical hormones on vascular tone, the hormones rendering a person more sensitive to renin.

There have been a few reports of notable bilateral hypertrophy of the adrenal cortex in children; some showed features of pseudohermaphroditism, and others were normal. In a case reported by Skelton (1945) there were signs of a vascular disturbance; extreme pallor ushered in the disease. In none of the reported cases was the blood pressure recorded.

Biopsy and Clinical Studies.—The frequent association of adrenal tumors and hypertension was noted by Castleman and Smithwick (1943). In the course of splanchnic resections for hypertension in 100 selected patients eight adrenal tumors were found in 7 patients; six were cortical adenomas and two were pheochromocytomas which had not caused paroxysmal attacks of hypertension. The authors also concluded that the morphologic evidence of renal vascular disease in more than half the cases was inadequate as the sole factor producing the hypertension and that the hypertensive state antedated the renal lesion. Many years ago Oppenheimer and Fishberg (1924) also found cortical adenomas more common in hypertensive patients, and Aubertin and Ambard (1939) noted that of 8 persons with hypertension 4 had diffuse cortical hyperplasia and 3 others adenoma of the adrenal cortex.

Hypertension due to tumors of the adrenal gland is not a great rarity. The hypertension due to tumors derived from the medulla (pheochromocytoma or paraganglioma) is usually paroxysmal but may on rare occasions be persistent (case report in the *New England Journal of Medicine*, 1944); it is different clinically and is clearly due to periodic release of epinephrine from the abnormally proliferating medullary tissue. Of interest in this connection is the demonstration by Vogt that injections of epinephrine hydrochloride (in doses which may be liberated in the body when the splanchnic nerves are stimulated) produce an output of cortical hormone into the blood; there is a relation between the adrenal medulla and the adrenal cortex.

As far as the adrenal cortex is concerned, carcinoma or adenoma may cause hypertension which is generally associated with the other constitutional manifestations of the hormonal activity of the tumor. The ele-

vated blood pressure returns to normal after the removal of the tumor (Boyd 1940); for example, hypertension forming part of Cushing's syndrome or the adrenocortical syndrome has been cured in a number of instances by operation.

The fact that tumor of the cortex produces chronic hypertension without impairment of renal function necessitates the consideration that hyperactivity of the cortex is concerned in the pathogenesis of hypertensive vascular disease and other conditions in which hypertension is a feature, in much the same way as diminished cortical function is accompanied with hypotension.

In hypercorticoadrenalism (adrenogenital syndrome) due, for example, to tumors as well as in virilism, hypertension is often present and is not of the paroxysmal type. Tumor or hyperplasia in children may lead to the clinical picture known as pubertas precox, which in some instances is associated with hypertension. Several steroids have been shown to be capable of inducing persistent hypertension in rats. Since abnormalities in sterol metabolism are known to occur in patients with the adrenogenital syndrome, the hypertension of this disorder may be due to the elaboration of such steroids by the abnormal adrenal tissue.

In Cushing's syndrome, a disease which occurs at any age and even in young children (the youngest patient reported on was only 11 weeks old) the clinical picture is most often dominated by features other than the hypertension; the hypertension may however be extremely severe and even enter the malignant phase, with hypertensive neuroretinopathy and necrosis of the renal arterioles. At present it is widely accepted that both pituitary and adrenal mechanisms are probably involved, though cases in which the condition is associated with carcinoma of the thymus are not easily explained. Occasional cases in which there were no visible adrenal changes have been described, as in recent reports by Heinbecker (1944) and McLetchie (1944).

The most plausible explanation here is that the adrenal cortex produces excessive quantities of ketosteroid and other hormones, but without any anatomic changes. Those hormones which accelerate gluconeogenesis from protein are regarded as important by Albright (1942); Cushing's syndrome is thus regarded as a hyperadrenocorticism with respect to the "sugar hormone." It is interesting to note that the blood sodium as well as the blood glucose is increased in Cushing's syndrome and in cases of adrenocortical tumor while the potassium content is decreased. Albright, with his tentative theory implicating the adrenal cortex in Cushing's syndrome, offered no explanation for the hypertension. The hematologic manifestations of Cushing's syndrome have been shown to be similar to those of the initial reaction of the body to nonspecific damaging agents ("adaptation syndrome" of Selye), and it has been suggested that the

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hormone alterations in Cushing's syndrome are similar to those in the early phases of the "adaptation syndrome" (de la Balze, Reifenstein and Albright, 1946). Selye's work on nephrosclerosis and hypertension in experimental animals is referred to later.

Heinbecker expressed the opinion that the hyaline changes in the pituitary basophil cells described by Crooke are degenerative and always secondary to some other lesion, either adrenal hyperplasia or hypothalamic atrophy. They are seen also in hypertension not clearly due to Cushing's disease. He found incidentally that there was considerable occlusive disease of the renal vessels in 3 of 4 cases which he considered adequate to explain the development of hypertension; no observations on the adrenal vessels were reported.

In a large majority of cases of Cushing's syndrome there is tumor (Oppenheimer, 1935) or hyperplasia of the adrenal cortex, and the condition can be cured by surgical intervention. Thus in a case in which

TABLE 1.—*Changes in the Adrenal Cortex in Association with Arterial Hypertension*

Author	Changes in the Adrenal Cortex
Philpot (1909)	Mean weight increased
Oppenheimer and Fishberg (1924)	Cortical adenomas more common in hypertensive patients
Aubertin and Ambard (1939)	Of 8 persons with hypertension, 4 had diffuse cortical hyperplasia and 3 others adenomas
Rinehart and others (1941)	Adenomatous hyperplasia almost regularly found; also an increase of mean combined weight
Sarason (1943)	Cortical enlargement, with increased amount of lipid
Castleman and Smithwick (1943)	Among 100 patients with hypertension 8 adrenal tumors were found in 7
Russi and others (1945)	Benign adenomas present in at least 1.45 per cent of 9,000 routine autopsies; hypertension and diabetes five times more common in persons with cortical adenomas

the condition was due to adrenal carcinoma remarkable improvement followed removal of the tumor, with a disappearance of the abnormal features, including the raised blood pressure (Silver, 1940).

In Cushing's disease, therefore, as in the adrenogenital syndrome there is evidence of adrenal dysfunction, with the production of abnormal steroids. The estrogenic and androgenic action of the urine in patients with these diseases has been demonstrated and a variety of abnormal steroids isolated from the urine. The development of the hypertension may be attributed to the action of these abnormal steroids. The adrenal glands should be studied in every case by palpation, pyelography or perirenal insufflation of gas. If the urinary excretion of 17-ketosteroids is greatly increased, surgical exploration is probably justified as an adrenal carcinoma may be present in spite of failure to demonstrate it clinically. There is also the possibility that increased excretion of other substances from the adrenal cortex may occur in the urine; this is discussed in a later section.

It has already been stated that in animals sustained experimental hypertension can be produced even after complete removal of one adrenal

gland and destruction of the medulla of the other gland. De Courcy (1934) obtained successful reduction of the systolic and diastolic pressures which lasted for months by performing subtotal bilateral adrenalectomy in patients with hypertension; one fourth of one adrenal gland is fully sufficient for all demands of the normal person. In a discussion on the surgical treatment of arterial hypertension, Paterson Ross (1940) admitted that there are grounds for removal of the adrenal cortex in man were it not for the danger of total adrenalectomy.

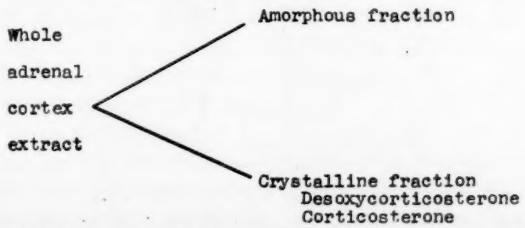
In table 1 is a summary of the changes found in the adrenal cortex in association with arterial hypertension.

D. ADRENAL CORTEX HORMONES AND THEIR FUNCTIONS

There are at present many theories concerning the functions of the adrenal cortex. Conceptions differ as to what are primary functions and what are secondary effects dependent on such functions.

The cortex is rich in globules of cholesterol esters and other fats. In addition to steroids, there are a number of other compounds present in high concentration in the gland. Sulfur is present, chiefly as glutathione. Choline and vitamins (A, B_1, B_2 and ascorbic acid) are also present. Long (1946) has recently brought forward evidence that cholesterol is the reserve steroid material from which "cortical hormone" is formed and then excreted with ascorbic acid.

Until the actual hormones have been definitely established, it is unlikely that any final decision can be made. Not all the hormones have been isolated, for the amorphous fraction which remains after the known crystalline steroid hormones have been removed from extract concentrates is extremely potent in its effect on the distribution of electrolytes; it also maintains normal renal function and normal rate of growth.



The elaboration and secretion of hormones by the adrenal cortex is controlled by the adrenocorticotrophic hormone produced by the cells of the anterior lobe of the pituitary gland. As a matter of fact, it appears probable that there are three different pituitary corticotrophic principles which stimulate the androgenic, "salt-active" and "sugar-active" hormones of the adrenal cortex (Selye 1944). During the "general adaptation syndrome" only the last two appear to be increased.

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It is important to observe that the various activities of the adrenal cortex are dissociable, as shown by the fact that the active substances isolated from the gland have many different physiologic actions.

About thirty steroids have been isolated from the gland. Not all have been shown to have biologic activity. At least six compounds with "cortin-like" activity have been isolated as crystalline substances from extracts, though more will probably be found since the residue still contains half the original potency. Only one of these crystalline compounds, desoxycorticosterone, is available commercially.

The adrenal cortex contains substances which have estrogenic, progestational, androgenic and sodium-conserving functions, others which play a role in the intermediate metabolism of carbohydrate and protein and a derivative which is concerned with lactation. None of the isolated compounds possesses all these functions. The functions of the various steroids may be disturbed in different degree and various clinical disorders produced.

It is of interest that the administration of estradiol, progesterone, testosterone and desoxycorticosterone to normal rats induces an elevation of the blood pressure in some animals to hypertensive levels.

While it is true that adrenal cortex tumors can induce virilism, the stimulation of certain tissues in that condition is probably due to (*a*) excess of a certain cortical hormone or of a degradation product of it or (*b*) a metabolic variant with androgenic and other properties. As further evidence that the disturbance in virilism may not represent true adrenocortical overfunction is the attempt of Grollman (1936) to relate the activity of the adrenal glands in virilism to the function of a special inner "androgenic" zone distinct from the interrenal tissue or the cortex proper. In the mouse at certain stages there is a prominent zone of epithelial tissue, the juxtamedullary or X zone, between the medulla and the cortex proper which has a different character from the cortex and appears to be associated with sex. A similar zone is present in the human fetus, and Grollman claimed that virilism in the female results from resurrection of this tissue. Broster and Vines (1933) stated that the cortical cells of the male fetus present fuchsinophil substance from the tenth to the seventeenth week whereas this substance disappears much earlier in the female fetus. There is fairly convincing evidence that the gonadotrophic luteinizing hormone produced by the basophil cells of the hypophysis stimulates the adrenal cortex, probably the X zone, to produce in both sexes androgenic hormones similar to testosterone (Reifenstein, 1944). Levy Simpson has pointed out that in the adrenogenital syndrome the cells undergoing hyperplasia probably differ from those producing the "life-preserving" cortical hormone, since adrenal hypofunction (Addison's disease) may coincidently complicate the picture, just as hypertension may be a feature of this syndrome.

In some circumstances certain cortical hormones necessary for the maintenance of normal blood pressure may be responsible in association with other factors for the production and maintenance of hypertension.

Effect of Desoxycorticosterone in Man.—Cortical extracts even in massive doses do not induce persistent or transient hypertension in either men or animals, probably because of the presence of numerous factors some of which may have opposite and regulatory actions.

Overdosage with desoxycorticosterone, however, in the treatment of Addison's disease, especially when the salt intake is high, can cause hypertension, edema, rapid gain in weight, congestive heart failure and an increase in plasma volume, venous pressure and extracellular body fluid (Ferrebee and others, 1939; Soffer and others, 1940; Thorn and others, 1942; McGavack, 1941). Particularly noteworthy is the appreciable rise in diastolic pressure. In some instances hypertensive levels may be obtained, without restoration of patients to normal activity (Ferrebee and others, 1939; Thorn and Firor, 1940; Cleghorn and others, 1939). Reduction of the dose of desoxycorticosterone and restriction of sodium intake will cause the hypertension to disappear.

Perera and others (1944) found that in patients with Addison's disease and without adrenal disease there was progressive elevation of the blood pressure to levels above normal with prolonged administration of desoxycorticosterone. The appearance of hypertension could not be correlated with abnormal retention of sodium, with an increased circulating blood volume or with an abnormally labile peripheral vascular system. Loeb has suggested that since in some cases of Addison's disease the use of salt alone may elevate the blood pressure above normal the action of desoxycorticosterone may be merely due to an ion effect on the blood vessels. Swingle and his co-workers (1941) have suggested that this steroid may perhaps affect the tone of the arterioles. Certain other workers found that the elevation of the blood pressure following the administration of desoxycorticosterone could not be correlated with excessive retention of salt water in the circulating blood or with a labile vascular system as manifested by a positive reaction to the cold pressor test.

It would appear from all the evidence that desoxycorticosterone acts directly or indirectly on the peripheral vascular system and that the hypertension induced by it is apparently a specific function of the hormone (Soffer, 1945), which is normally balanced by other fractions of the adrenal cortex.

The profound effect on the blood pressure and the distribution of electrolytes warrant the routine use of this hormone in all suspected cases of the Waterhouse-Friderichsen syndrome (Weinberg and McGavack, 1945).

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Effect of Desoxycorticosterone in Animals.—Administration of desoxycorticosterone acetate has been observed to increase the blood pressure above normal levels in adrenalectomized dogs (Swingle and others, 1941; Remington and his associates, 1941), in normal dogs (Swingle and others, 1941; Kuhlman and others, 1939; Rodbard and Freed, 1942), in normal rats (Briskin and others, 1943; Grollman and others, 1940) and in hypertensive animals (Rodbard and Freed, 1942).

In the domestic fowl large doses of desoxycorticosterone cause nephrosclerosis, with hyalinization of the capillaries of the glomerular tuft, generalized tissue edema and cardiovascular changes (Selye, 1942). Large doses of sodium chloride added to their drinking water may be sufficient to elicit these changes (Selye, 1943). Selye and Hall (1944) administered excessive doses of desoxycorticosterone and sodium chloride to male rats and produced nephrosclerosis, renal arteriolar hypertrophy, hyaline casts in the renal tubules and pronounced cardiac hypertrophy. These findings suggest a possible causal role of adrenal cortical hyperactivity in the production of nephrosclerosis, "renal" hypertension and hypertensive heart disease in man.

Both desoxycorticosterone acetate (D.O.C.A.) and lyophilized anterior pituitary tissue (L.A.P.) produce malignant hypertension, nephrosclerosis, polyarteritis nodosa of the cardiac vessels and myocarditis; lyophilized anterior pituitary tissue probably causes the adrenal cortex to elaborate desoxycorticosterone, like cortical hormones (Selye, 1946; Hall and others, 1946). Adrenalectomy prevents these effects. Selye (1946) advanced the theory that the spontaneous diseases of man such as those produced by overdosage of lyophilized anterior pituitary tissue and desoxycorticosterone are due to a defensive increase in the production of the adrenocorticotrophic and cortical hormones, the cardiovascular lesions being therefore by-products of this adaptive defence reaction, i.e., diseases of adaptation.

Grollman and others (1940) suggested that the hypertensive action of desoxycorticosterone is due to renal damage. Swingle and others (1941) and Leathem and Drill (1944), however, produced evidence against a toxic action on the kidney as a causative factor in the hypertension induced by this hormone.

Knowlton and his associates (1946) produced striking hypertension with use of desoxycorticosterone acetate in rats with cytotoxic serum nephritis, but no rise was observed in non-nephritic rats given the same doses of desoxycorticosterone or in nephritic animals which did not receive it. Administration of desoxycorticosterone caused a specific renal lesion in the tubules of all animals. The authors could not explain the mechanism responsible for the development of hypertension and the augmentation of the nephritic process.

From experiments on rats, Gaudino (1945) concluded that adrenal cortex tissue or its hormones (desoxycorticosterone, or 17-hydroxy-11-dehydrocorticosterone) are necessary for the existence of renal hypertension and for the maintenance of normal arterial pressure.

Effect of Other Hormones.—The pressor action shown by desoxycorticosterone is also exhibited by many other active hormonal substances. As a matter of fact, various commonly used steroids are capable of inducing hypertension in experimental animals. This suggests that the hypertension observed in certain endocrine disorders such as Cushing's syndrome and the adrenogenital syndrome may be due to the production of excessive amounts of normally occurring steroids or to abnormal steroid compounds.

It has already been mentioned that estradiol, testosterone, progesterone and desoxycorticosterone can produce hypertension in rats. It is of interest that the last two hormones and estrogenic and androgenic compounds are present in the adrenal cortex.

Daily intramuscular injections of diethylstilbestrol into normal rats or feeding with stilbestrol produced a gradual rise of systolic blood pressure, which reached hypertensive levels in many cases (Leathem and Drill, 1943; Grollman, 1940; Sapeika, 1948); this pressure response may be due to the adrenal glands, which were found to be much hypertrophied, or to an action on the kidney the function of which may be altered by steroids (Selye, 1939). The mode of action of large doses of stilbestrol in causing hypertension is not yet properly understood.

Estrogens in large doses inhibit anterior pituitary activity so that the signs of hypophysectomy are produced with the exception that the adrenal cortex does not atrophy and may actually become enlarged.

These effects which have just been described are produced in animals. In human beings, administration of estrogens often relieves the vasomotor and nervous changes at the menopause, and in the doses ordinarily used, doses far smaller than those (1 mg. daily for a rat) administered to produce hypertension, it aids in restoring equilibrium and thus often reduces the blood pressure. The small doses of estrogen given for hypertension developing during the menopause is believed to act through inhibition of the anterior pituitary gland, overfunction of which occurs with the diminution of ovarian function; therefore any overfunction of the adrenal cortex at this time would also be indirectly inhibited by administration of estrogens. There are certain tumors of the ovary which produce excessive amounts of hormone, for example, the granulosa cell tumor which produces remarkably large quantities of estrogen, leading to precocious puberty and "feminization," and the arrhenoblastoma which produces large quantities of androgen. These do not appear to

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cause any striking change in the blood pressure. A study of reports on these tumors failed to reveal any reference to the blood pressure levels.

Prolonged administration of large doses of diethylstilbestrol has been reported by Karnaky (1945) to produce no untoward effects except uterine bleeding. However, severe hepatic damage has occurred after moderate dosage (Elias and Schwimmer, 1945).

Estrogens in huge doses are reported to be of value in controlling toxemias of pregnancy in patients with diabetes mellitus.

a—c Bodies (Raab).—Raab (1941) has made determinations of adrenal hormonal compounds (ephinephrine and cortical steroids, a—c bodies) in the human blood. The significance of such determinations is as yet not clearly defined. He could find no clear relation between the level of adrenocortical compounds and that of the blood pressure, but an abnormally high level of the compounds was found in a number of persons with renal hypertension. He found a much higher circulating level of adrenocortical compounds after muscular exercise in patients with essential hypertension than in normal subjects, and he regarded this tendency as the decisive factor in the development of arteriosclerosis and consequent ischemia of the vasomotor centers. Bruger and others (1944) stated that these a—c bodies do not increase quantitatively in the blood when the blood pressure is elevated during the cold pressor test in human beings or after the injection of renin in cats; there is, however, a close correlation between the rise in blood pressure and the concentration of a—c bodies in the blood of animals after the intravenous injection of epinephrine. In their study of these a—c bodies in normontensive and hypertensive human subjects they found the difference between the two groups to statistically nonsignificant.

E. URINARY EXCRETORY PRODUCTS OF ADRENAL CORTEX HORMONES AS AN INDEX OF ADRENOCORTICAL ACTIVITY

There are several methods for the determination of the potency of adrenal cortex extracts, based on the correction of physiologic changes which occur in the animal after adrenalectomy. For example, the profound changes in electrolyte metabolism, with short survival after the operation, markedly impaired muscle efficiency and hepatic gluconeogenesis, have been used as the basis for various methods of assay.

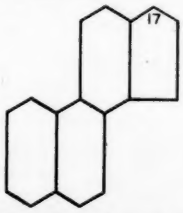
The adrenocortical hormones are rapidly inactivated in the animal body, and their excretory products are different from the original substances. Among the urinary steroids are androgens, estrogens and "cortins" and also physiologically inactive substances which in certain instances are more reliable as an index of hormone excretion than is the biologic activity found in urine.

In recent years it has been shown that certain aspects of adrenocortical activity in human beings may be measured by assays of certain urinary excretory products, corticoid substances and the 17-ketosteroids. The methods have proved useful but are not easy to perform.

It is recognized that excretion is not necessarily a measure of secretion and that increased hormone production may occur without an abnormally large amount appearing in the urine. However the extent to which the excretion of corticoid substances and the 17-ketosteroids, together or independently, will vary, may indicate possible types of adrenal secretion in various pathologic conditions. Selye (1946) pointed out that the immediate influence of certain stimuli, "alarming agents," is to eliminate the 17-ketosteroid and androgenic compounds present in the adrenal cortex together with the adrenocortical hormones (corticoids) but that later the gland produces only, or at least predominantly, adrenocortical hormones.

The concentration of ketosteroids in the urine as an index of adrenal cortex function is less specific than the concentration of cortin-like material since the gonads also may contribute to the total ketosteroid value. The partition of gonadal and adrenocortical hormonal derivatives of normal, endocrinopathic and cancerous patients has recently been reviewed by Salter and others (1946).

1. *The Urinary* 17-*Ketosteroids.*—The significance of these recently discovered substances in the urine is still not fully investigated. These substances, whose exact precursors are not yet known, are excretory transformation products of the metabolism of steroids whose source is chiefly the adrenal cortex and the testis and are an index of the secretory activity of these endocrine organs. They do not possess measurable corticoid activity in the usual biologic tests. The term 17-ketosteroid (Callow, 1940) is applied in general to a group of compounds which give a certain type of color reaction and are so named because of a ketone group at the 17 position on the complex sterol molecule.

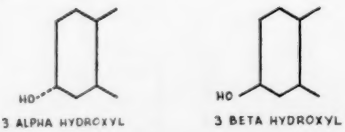


The terms 17-ketosteroid and androgen are often confused. Not all 17-ketosteroids are androgens, nor are all androgens 17-ketosteroids.

It is becoming increasingly apparent that the quantities of androgen or 17-ketosteroid excretion are measures less of testicular endocrine function than of the activity of the adrenal cortex (Callow, 1940).

The 17-ketosteroids are considered to be chiefly indicative of adrenal cortex activity because (*a*) they are lacking or present in only small amount in the urine in Addison's disease (Salter and others, 1946), (*b*) they are excreted in large amounts from certain active adrenal tumors and (*c*) they are excreted in nearly normal amount by castrated men and ovariectomized women, which demonstrates only a small contribution to their production by the gonads. It may be pointed out here that in cases of ovarian tumors, i.e., granulosa cell tumor and arrhenoblastoma, which produce large amounts of estrogen and androgen respectively, the output of 17-ketosteroid is normal. It has been estimated that a normal man excretes about 14 mg. of 17-ketosteroids daily while the level for women is about 9 mg. Castration in the male reduced 17-ketosteroid excretion to the female level, while total loss of adrenal cortex function in Addison's disease decreases the level for both sexes to near zero. In cases of panhypopituitarism there is little or no 17-ketosteroid in the urine because of atrophy of both testes and of the adrenal cortex. Consequently the estimation has been made by Fraser and others (1941) that of the total daily excretion of 17-ketosteroids of 14 mg., 9 mg. has is origin in the adrenal cortex in both sexes while 5 mg. is derived from the Leydig cells of the testes and none from the ovaries. The daily fluctuations in normal circumstances are not great, so that one or two accurately timed and collected twelve-hour or twenty-hour specimens of urine are sufficient for most clinical diagnostic purposes (Talbot and Butler, 1942). Normal children under 7 years of age excrete negligible amounts of hormone (Talbot and others, 1940).

In certain diseases it appears to be valuable to separate the total neutral ketosteroids into alpha alcoholic, beta alcoholic and nonalcoholic fractions, as alterations in the ratio of these ketosteroids may exist. Procedures suitable for use in hospital laboratories have been described (Talbot and others, 1940 and 1941; Bauman and Metzger, 1940; Cahen and Salter, 1944). The terms alpha and beta refer to the spatial position of the 3-hydroxyl group (Fieser, 1937).



Available evidence indicates that whereas the alpha neutral ketosteroids probably arise from the adrenal and gonadal secretions, the beta neutral ketosteroids are an excretion product only of the cells of the adrenal cortex. They form a small percentage of the normal total daily output. The average values for normal persons as recently published (Salter and others, 1946) are as follows: for the 3-cis (β) hydroxyl frac-

tion, 1.3 mg. per day; for the female 3-trans (α) hydroxyl fraction, 6.3 mg. per day, and for the male 3-trans (α) fraction, 12.9 mg. per day.

Unusually large amounts of the beta form are excreted in cases of adrenal tumor (Crooke and Callow, 1939; Talbot and others, 1942). Recent evidence suggests that only two beta 17-ketosteroids exist in significant amounts in the neutral fraction of urine extracts (Callow, 1939; Butler and Marrian, 1938). The first is dehydroisoandrosterone, an androgen present in small amounts in normal urine (Callow, 1939; Koch, 1937), and the second is isoandrosterone. The adrenal origin of dehydroisoandrosterone seems well established, and estimation of this substance in the urine might indirectly measure one function of the adrenal cortex. In most human subjects, normal or diseased, the role of dehydroisoandrosterone is relatively small, but it is of more significance in adrenocortical tumors (Salter and others, 1946).

Assay of urinary 17-ketosteroids may thus provide diagnostic information helpful in detecting hyperfunction or hypofunction of the adrenal cortex. In the urine of patients with adrenal hyperplasia and cortical tumors there are not only a great number of ketosteroids not found in normal urine but also a distinct difference in the pattern of their distribution. Evidence of chronic adrenocortical deficiency may be obtained from the biochemical picture of the blood, special diagnostic procedures, e.g., maintenance of a low sodium chloride intake, or decreased urinary 17-ketosteriods (Sharpey-Schafer, 1944; Reifenstein, 1944). In the adrenogenital syndrome grossly increased excretion of 17-ketosteroids or androgen favors the diagnosis of a tumor. In this condition the gland presumably secretes an abnormal product for reasons already given and also since the syndrome cannot be produced by the use of massive doses of cortical extract. In cases of masculinizing tumors values as high as 176 and 166 mg. daily and even higher have been recorded (Talbot and others, 1940; Fraser and his co-workers, 1941; Talbot and others, 1941). In cases of postpubertal tumor the output may vary from 40 to 325 mg. or more per day ("British Encyclopedia of Medical Practice," 1944, p. 54; Scowen and Warren, 1946). In Cushing's syndrome the values are sometimes increased above normal.

Administration of desoxycorticosterone acetate to normal persons of either sex did not increase their excretion of 17-ketosteroid (Cuyler and others, 1942).

The fact that an excess of total 17-ketosteroids may be excreted daily in the urine of patients with adrenocortical hyperplasia or actual tumor in whom there is little or no elevation of the blood pressure and the fact that a "pressor" steroid like desoxycorticosterone causes no increase in the excretion of 17-ketosteroid, would suggest that estimation of these products can be of no help in determining the role of the adrenal cortex

in the pathogenesis of hypertension. Bruger and others (1944) found that hypertensive women (chosen because in them the entire amount of 17-ketosteroid excreted appears to be derived from the adrenal cortx) tend to excrete less 17-ketosteroids in the urine than normal subjects, which they suggested may indicate a hypofunctioning adrenal cortex in patients with hypertension, reflecting perhaps a gland exhausted under the constant strain put on it by the persistent elevation in blood pressure. Another explanation, based on Selye's work, is that the lowered ketosteroid excretion may represent a "shift" in the production of hormones by the adrenal cortex; while this gland produces excessive amounts of "corticoids," it may not be able to elaborate the normal quantity of "testoids." It has still to be demonstrated what the urinary output of other adrenocortical substances is in arterial hypertension.

It is possible that further characterization and identification of the urinary steroids will result in the discovery of compounds which will indicate some of the lesser known or unknown functions of the adrenal cortex.

2. *Cortical-like Material.*—The "cortin-like" properties of extracts of urine from various sources have been demonstrated by several investigators. Thus, Dorfman and his associates (1942, 1944) have demonstrated that normal human urine contains adrenal-cortex-like material, a complex mixture of substances, which will exert a biologic effect similar to those of the adrenal steroids; when administered to adrenalectomized rats, the urine extract maintains life, protects the animals against death from cold and has glycogenic properties. The active material is in the ketonic neutral fraction, and at least a portion appears to be in a combined form. It does not give the color reaction for 17-ketosteroids.

Other workers have also demonstrated that extracts of urine contain cortical-like material (Perla and Gottesman, 1931; Grollman and Firor, 1932; Weil and Browne, 1939). Cortical steroid-like material has been shown to be present in greater amounts in the urine obtained from patients after operation (Venning and others, 1944) than in the urine of normal men. Cortin-like material could only be demonstrated once in samples of urine from 7 patients with Addison's disease (Dorfman and others, 1944).

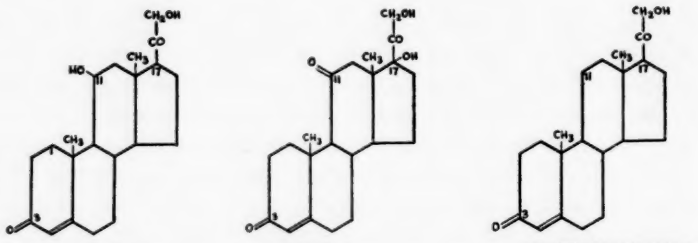
Vogt (1943) could not detect cortical material in the arterial blood of various animals or in blood from the right side of the heart; this indicates that the body disposes at great speed of the hormone released from the gland. She concluded that renal excretion plays a minor role in the disposal of cortical hormone. The liver, spleen and gastrointestinal tract were found to be unessential for this rapid inactivation of the hormone. An amount of cortical hormone detectable by biologic assay was, however, present in the venous blood leaving the adrenals, its quan-

tity being surprisingly high. As far as could be detected, the minute output by the adrenal cortex was not affected by changes in the blood pressure or in the blood flow. An injection of epinephrine greatly increased the output per minute of cortical hormone, and repeated injections caused an increase in weight of the adrenals associated wtih lipid storage; this did not occur after hypophysectomy (Vogt, 1944). The adrenal glands are extremely vascular, and the functions of cortex and medulla may be influenced by their intimate vascular relationships.

It seems justified, from the investigations of Dorfman and others, to conclude that the active urinary cortical-like substances are metabolites of adrenal cortex steroids and that variations in this urinary content reflect the physiologic activity of the gland. Although only incomplete data are available at present, the behavior of these substances on partition between various solvents and the possession of a reactive group relates them chemically to the known biologically active steroids of the adrenal cortex. Indirect evidence of the adrenal origin of these substances is provided by consideration of the amounts present in the urine in different circumstances. Thus the urine of man after exposure to stress, burns, infections and operations contains three to thirty times the amount of cortin-like material that is excreted by normal persons. In rats under similar conditions of stress the adrenal cortex loses its lipids and then hypertrophies, which indicates indirectly that there has been increased secretory activity. As pointed out previously, Selye (1946) stated that immediately after a stimulus (an alarming agent) 17-ketosteroids and androgens are eliminated together with adrenocortical hormones by the adrenal cortex but later the adrenocortical hormones are predominantly produced.

Few experiments have been reported on the detection of biologically active substances in the urine after the administration of adrenal cortex steroids. Some workers (Venning, Hoffman and Browne, 1944) have shown that approximately 10 per cent of the biologically active substances of an adrenal cortex extract injected intravenously in man and in the dog is recoverable from the urine.

Ready identification of the urinary corticosteroids may offer a new insight into the workings of the complex adrenal cortex factory. The urinary substances which have definite corticoid activity on biologic assay as measured by their effect on carbohydrate metabolism and muscle function are cortical steroids having an oxygen atom at position 11 on the steroid skeleton, e.g., corticosterone and 17-hydroxydehydrocorticosterone, whereas desoxycorticosterone is especially effective in maintaining the life of adrenalectomized rats, including those exposed to cold.



Recently, Dorfman and his collaborators (1946) showed by their assay method in rats that a pooled sample of male urine contained activity the equivalent of 0.6 mg. of 11-dehydrocorticosterone per liter.

A new chemical method that estimates both active and partially reduced corticosteroids in urine has recently been published (Lowenstein, Corcoran and Page, 1946). The average excretion in normal males was found to be 0.5 to 0.8 mg. per twenty-four hours, expressed as dehydrocorticosterone; a level of 0.15 mg. was found in a case of Addison's disease and a level of 21 mg. in one of Cushing's syndrome.

Comparison of Cortical-like Material and 17-*Ketosteroids.*—The concentration of cortin-like material in the urine may serve, as already suggested, as a specific index of cortical function. These substances and a number of closely related steroids were first isolated from adrenal gland extracts and later demonstrated to be present in the complex mixture of substances extractable from the urine by the solvents.

Although variations in the excretion of 17-ketosteroids also to a certain degree reflect adrenal cortex activity, the parallelism is rather crude. These urinary 17-ketosteroids are different both chemically and biologically, e.g., androsterone, dehydroisoandrosterone, and androsterone-17. They typically lack the ketol side chain at C 17 characteristic of the hormonally active adrenocortical steroids and also lack the ketone group at C 3 (see formulas given previously). They contain 19 carbon atoms whereas the adrenal substances contain 21 carbon atoms per molecule. They do not possess measurable corticoid activity in the usual biologic tests. Their chemical constitution suggests that they are metabolic products of more active substances, i.e., they may be reduction products of corticosteroids. They are excreted as esters, detoxified material, whereas the active urinary "cortin" is apparently not conjugated or at least only a portion appears to be in the combined form. The 17-ketosteroids have still to be properly sorted out and the contributing sources identified. Their exact precursors are not yet known so that they may be considered as general indicators of adrenal cortex secretion rather than products of specific cortex hormones. These compounds

arise only in part from the adrenal glands, and in fact there may be additional sources other than the gonads.

COMMENT

The Renal Pressor Mechanism.—There is little doubt that after the constriction of one or both renal arteries a chemical agent, renin, is produced, which then leads to a state of hypertension. There has been much evidence of participation of the renal pressor system in the genesis of hypertension, but there is also evidence from certain studies in both animals and human beings at variance with this belief (Goldblatt, 1947). The initial cause for the secretion of this chemical substance in arterial hypertension itself and the nature of the chemical agent have not yet been clearly demonstrated. Renin appears to be normally concerned with the regulation of blood pressure rather than with the maintenance of normal blood pressure. The presence of the components of the renal pressor system, renin, renin activator and renin inhibitor, in normal subjects suggests, on teleologic grounds, some function of this system in normal physiology.

The development of tachyphylaxis to this substance renin without the occurrence of a corresponding decrease in arterial pressure makes it doubtful whether it can be responsible for a persistently raised blood pressure. In hypertensive vascular disease, careful search has failed to reveal the reason for the elevated diastolic pressure, the cause for the generalized arteriolar constriction which is manifest clinically as hypertension.

The view that a "renal factor" is the cause appears to be less popular as the evidence for it grows more complex (Goldring and Chasis, 1944; Smith, H. W., 1943). Although an obscure metabolic fault in the kidneys may eventually be incriminated, it is doubtful that renal ischemia as such is really responsible for the genesis of hypertension, even after consideration of such direct experimental approaches in man as the work of Dexter and Haynes (1944) and of Quinby and others (1945), dealt with in a previous section. The former workers concluded that the renin-pressor mechanism may be involved only initially in the development of hypertension.

It is doubtful whether a state of ischemia exists early in patients with hypertensive vascular disease sufficient to abolish the functional capacity of an enzymatic oxidative system in the kidneys. The decrease in renal blood flow and the elevation of filtration fraction occur earliest in the disease and appear to precede a decrease in the functional capacity of the renal tubules (Goldring and Chasis, 1944; Bradley, 1944).

In a study of the changes in hypertension and in renal function following unilateral nephrectomy, Friedman and others (1942) found that in none of their cases was there a complete return of the blood pressure to normal despite the fact that in 3 patients there was no "ischemia" of the remaining kidney. They concluded that renal ischemia may be a concomitant but not necessarily a causative factor in the pathogenesis of human hypertension.

According to Gubner and others (1946), in a review of the etiology of hypertension, there is no evidence that the renal pressor system plays a part in the initial stages of hypertensive vascular disease. They stated that the basal blood pressure, which may largely be determined by the humoral renal pressor mechanism, is normal in the earlier stages of hypertension. The humoral component may be important in the later stages when organic lesions in the renal (and other) arteries develop. Their suggestion is that neurogenic (vasomotor) components are responsible for the elevation of the blood pressure in the earlier stages of hypertensive vascular disease, attributed largely to psychosomatic influences.

In discussing the etiology of hypertensive vascular disease in a recent book, Herndon (1946) expressed the opinion that the mechanism is of humoral origin, since the process is reversible and denervation does not abolish it. It can arise from disease of the kidney, but this is not the general rule. The increased vascular resistance is not due primarily to organic changes in the vessel walls. The renal origin of hypertension is unproved.

From studies on dogs over a period of years, Grollman (1946) reported that chronic hypertension is not the result of liberation of a pressor substance by an ischemic or otherwise injured kidney, since removal of the constricted kidney fails to abolish it and the blood pressure is maintained even in the absence of all renal tissue. He stated that in experimental hypertension there is an acute rise probably due to tissue necrosis induced by "renal ischemia" but that the permanent rise which constitutes chronic hypertension requires weeks for its appearance and does not need the presence of renal tissue. To explain these findings, Grollman assumed that the kidney normally has a humoral function, interference in which by nephrectomy, constriction, ischemia or toxic agents results in a deficiency which is responsible for the observed rise in blood pressure.

The work of Selye (1946) already referred to shows that the nephrosclerosis and cardiovascular damage caused by anterior pituitary preparations and desoxycorticosterone is apparently not due to a direct action on the kidney and the cardiovascular system but is probably

mediated by the adrenal cortex, through the secretion of desoxycorticosterone-like compounds.

The Role of the Adrenal Glands.—The possible importance of the adrenal cortex in experimental "renal" hypertension (Goldblatt and others) was dealt with in a previous section. The possibility that adrenal ischemia may cause arterial hypertension has more recently been investigated by Victor (1945). In 6 dogs the application of ligatures around the vessels entering the left adrenal gland caused the systolic blood pressure to rise promptly from an average of 125 mm. of mercury to 225 mm. or more within two weeks. This hypertension was sustained in all the dogs for seven months (up to March 1946), comparable with the hypertension produced by experimental "renal ischemia" with the Goldblatt method. These results have been confirmed by Ogden and others (1948). The question now arises whether some methods of producing renal ischemia, with the ensuing hypertension, may not sometimes interfere with the blood flow through the adrenal glands, thus initiating changes which correspond with those following purposeful ligation of the adrenal vessels.

Evidence suggests that the endocrine system, like the nervous system, is of great importance in the genesis of certain types of hypertension, though probably subsidiary to other causes initiating the condition. Patients with hypertension do not commonly show obvious signs of endocrine dysfunction, but in animals ablation and other experiments clearly demonstrate the importance of the endocrine system, especially the adrenal cortex. In these cases possible modes of action might be: (1) that too much adrenocortical hormone is produced, (2) that too little of the hormone is broken down, or (3) that the end organ, e.g., blood vessels, is hypersensitive to stimulation by the hormone.

Normally under basal conditions the caliber of the peripheral arterioles is not known to be greatly modified by products of the endocrine glands except in the case of the adrenal cortex. The presence of an excess of adrenal cortex hormone, as of epinephrine, such as is found in the presence of tumors of the adrenal gland may result in hypertension of the "essential type," which is completely relieved by removal of the tumor.

It may be concluded that this gland, and its governing body, the hypophysis, is involved directly or indirectly in the mechanism which raises arterial pressure. Among others, the gland contains substances which have estrogenic, progestational, androgenic and sodium-conserving functions. It is interesting that estradiol, progesterone, testosterone and desoxycorticosterone will induce elevation of the blood pressure of normal rats to hypertensive levels. In hypercorticoadrenalism producing the adrenogenital syndrome and Cushing's disease the adrenal dysfunc-

tion may lead to the development of hypertension through the production of abnormal steroids; estrogens and androgens and a variety of abnormal steroids have been demonstrated in the urine of patients with this condition.

Enlargement of the adrenal glands in hypertensive conditions in man seems well established and appears to involve both cortical and medullary hyperplasia. It has still to be definitely shown whether the adrenal changes produce alterations in the cardiovascular system or develop secondarily to the hypertensive state. Much evidence favors the former view.

Perera (1945) reported an unusual and instructive case. A patient with hypertension in whom hypoadrenalism subsequently developed had persistent elevation of the blood pressure while receiving desoxycorticosterone. Administration of salt alone resulted in a fall of blood pressure to within normal limits although water and electrolyte balance was maintained. Perera suggested that the adrenal cortex may be important for the development or maintenance of hypertension.

The lack of knowledge concerning the relation of physiologic and pathologic processes in the cortex to circulatory disorders does not justify the assumption that cortical lesions are nonfunctional and clinically asymptomatic. The adrenal cortex may act in the following ways: (1) by its control over salt and water metabolism and the regulation of body fluid and blood volume, (2) by maintaining the responsiveness of the cardiovascular system to pressor substances in the blood or to other hypertensive stimuli or (3) by storing substances, i.e., lipid, protein, ascorbic acid, which are useful in the protection of the medullary hormone epinephrine against inactivation and destruction.

Cortical overactivity in hypertensive disease has been suggested by certain experimental and clinical observations cited already and is further suggested by certain associated metabolic abnormalities:

A. It is fair to say that retention of sodium chloride and water represents a significant contribution of cortical function to the maintenance or increase of blood pressure, although most of the other endocrine glands are also concerned in this process. The association of hypertension with retention of salt and water in adrenal, thyroid and pituitary disorders as well as in obesity and in toxemias of pregnancy is reviewed by Goldzieher (1944).

It has recently been found by Grollman and other (1945) that the administration of diets low in sodium content decidedly reduced the blood pressure of rats with experimental renal hypertension. They demonstrated, moreover, that the life of the animal was actually prolonged. In 2 of 6 hypertensive human subjects on a low sodium diet the blood

pressure was reduced to normal, with moderate reduction in 3 others and no decline in 1.

B. Hyperglycemia and reduced sugar tolerance are common in patients with renal hypertension or hypertensive vascular disease, according to von Noorden and Neubauer. Overactivity of adrenal cortex causes increased gluconeogenesis and decreased utilization of carbohydrate. These facts suggest that diabetes and hypertension may be coordinated and caused by the same influences. The frequent association of the two conditions appears more than coincidental. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general group (9,000 autopsies), and both diseases were frequently present in association with such tumors (Russi, 1945).

C. Hypercholesterolemia is demonstrable in at least 70 per cent of all cases of renal hypertension and hypertensive vascular disease; cholesterol metabolism and its abnormalities are closely related to the function of the adrenal cortex. The mechanism of sensitization of the walls of the blood vessels to hypertensin may possibly be related to the use by the adrenal cortex of blood lipids and especially of cholesterol.

Mention must be made of the important and now well established work of Selye (1936, 1944 and 1946) in regard to the probable role of the adrenal cortex in certain "diseases of adaptation," including hypertension. One of the most prominent morphologic changes in the "alarm reaction" is enlargement of the adrenal cortex due to hypertrophy of the individual cells and discharge of their lipid granules. True hyperplasia is usually less marked. This change is considered a sign of increased endocrine activity and takes several hours to develop; it continues to some extent as the organism becomes adapted to prolonged exposure to the stimuli (which may be of various kinds, e.g., cold, fever, forced exercise, drugs or toxic tissue extracts). It has long been suspected that hormones are important in adaptive processes. In the "general adaptation syndrome," which is the sum of the nonspecific, adaptive, pathologic and biochemical reactions, certain changes depend on the integrity of the hypophyis and the adrenal cortex.

In the reaction to continuous stress and strain, the anterior pituitary gland is actively engaged in producing an increase of corticotrophic hormone but elaborates less growth, lactogenic and gonadotrophic hormones. It appears that even the normal production of basic cortical hormone (corticoid) of the adrenal is enormous (Vogt, 1943), but during the alarm reaction phase of the general adaptation syndrome there is increased production of this hormone, according to Selye. This excess is produced under influence of the corticotrophic hormone and causes a number of secondary changes, especially in lymphatic organs, carbohydrate and electrolyte metabolism, the kidneys and the cardio-

vascular system. Since overdosage with desoxycorticosterone produces such changes (in animals) as hypertension, vascular lesions like polyarteritis nodosa, myocardial lesions and lesions of the joints and nephrosclerosis, the possibility has arisen that certain diseases of man might result from excessive production of endogenous "salt-active" adrenal cortex hormones. Selye expressed the belief that there is much evidence in favor of this interpretation; these hormones produced in response to stress may have deterimental side effects due to their inherent toxicity.

Recently Selye (1944) showed that anterior pituitary extracts can produce the same organic lesions as desoxycorticosterone, probably through the action of their corticotrophic factors releasing excess of desoxycorticosterone-like substances. On the experimental evidence, this would appear to be the most probable hormonal mechanism in the body. The final common hypophysioadrenal pathway could explain how the many different factors lead to the same end result.

Many natural hormones, especially the trophic hormones of the anterior pituitary gland, appear to be proteins. Proteins are certainly present in glandular extracts. These proteins can act as antigens and lead to antibody formation (antihormones). This suggests that the phenomena such as periarteritis nodosa, arthritis and renal lesions produced in lower animals may be due to an antibody antigen reaction. The same vascular reactions have been produced with the effector hormone desoxycorticosterone. No antihormone has so far been produced for an effector hormone like epinephrine or estradiol. The steroid hormones never form antihormones but may produce antibodies. Zondek and Bromberg (1945) suggested that in certain circumstances patients may react to hormones produced by their own endocrine glands; various steroids including desoxycorticosterone were investigated by these workers. Desoxycorticosterone administered to animals may perhaps combine with protein, and the resulting complex may act as an antigen, with sensitization of blood vessels then leading to vascular reactions. There is evidence, however, that in man polyarteritis nodosa can result from exposure to a variety of nonspecific agents and in animals it is possible to reproduce this condition by such nonspecific damage as exposure to cold (Selye and Pentz, 1943).

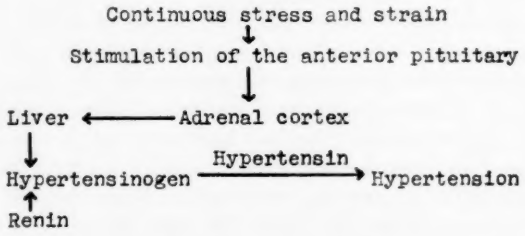
Experimental work has shown that the adrenal cortex is important in the production of hypertensinogen, probably stimulating its formation in the liver. The presence of the adrenal glands or the administration of desoxycorticosterone is essential for a normal hypertensinogen level in rats. The anterior pituitary gland and the adrenal cortex hormones may influence blood pressure directly through this mechanism, renal changes being independent of the high blood pressure or primary or secondary to it.

The different types of adrenal cortex hormones may be produced in different proportions selectively stimulated by different adrenocorticotrophic principles. This is emphasized also by Albright (1942) and by Goldzieher (1944). Thus desoxycorticosterone or some related active steroid may be selectively elaborated under the influence of adrenocorticotrophic stimuli.

The following mechanism is suggested by Selye:

Chronic exposure to stress
↓
Adrenocorticotrophic hormone
↓
Adrenal cortex
↓
Desoxycorticosterone or
pharmacologically related compounds
(overdosage)

The following schematic representation of the factors involved in the production of hypertension is suggested, based on the experimental work referred to in earlier sections of this work:



The concept that hyperfunction of the adrenal cortex may occur in the absence of demonstrable histologic changes is not disturbing since analogous endocrine paradoxes have been recognized for a long time and new ones have been described recently. For example, in cases of hyperthyroidism there is sometimes no evidence of hyperplasia when the gland is examined microscopically. Diabetes mellitus furnishes another example; few histopathologists would be willing to gage the severity of the disease by looking at the islets of Langerhans. The view has to be accepted that with the present relatively crude histologic technic the microscopic appearance of an endocrine structure may be an erroneous criterion of its secretory activity. The reverse problem also occurs. Thus, in recent literature there are two reports which indicate that functional adrenocortical insufficiency may occur in association with hyperplasia of the adrenal cortex (Wilkins and others, 1940; Dijkhuizen and Behr, 1939). In some cases the explanation may be that there is replacement of the interrenal tissue, notably the zona fasciculata, in which, according to Bennett's histochemical studies in the cat (1939), the cortical hormone is localized.

The Hypothalamic-Pituitary Mechanism.—Increasing attention is being paid to the psychosomatic factor in diseases peculiar to civilized man. Environmental influences such as the "alarming stimuli" (Selye), as well as heredity, play an unquestionable role in the genesis of hypertension. The emotional make-up of a person and the stresses imposed on him are believed to play a part in many cases of hypertension. The nervous element in patients with hypertensive vascular disease has long impressed clinicians, though psychologic disorders and the physiologic disorder hypertension may represent reflections of a basic failure foreshadowed early in life.

Recent studies indicate that the hormones of the adrenal cortex play a significant role when the organism encounters or is subjected to situations of stress. Hoagland and others (1946) have demonstrated that the stress of certain psychomotor activity ("pursuitmeter" operation under anoxic conditions) causes increased adrenal cortex secretion. Organic disease of the central nervous system in man and experimental interference with the nervous system in animals can produce elevated blood pressure (Dock and others 1942).

The hypothalamus must be considered in the pathogenesis of hypertension. Its crowded "centers" synthesize and supervise numerous functions. It regulates the production of hormones of the anterior pituitary gland, through whose trophic influence it controls other endocrine glands. The hypothalamic-pituitary unit may lead to atrophy or hyperplasia of these glands or to formation of adenoma in them; however, such changes are not necessarily present, and alteration of hormone production may develop without such anatomic glandular changes.

Disorders of hypothalamic origin, metabolic, endocrine and cardiovascular, arise from the numerous afferent stimuli which the hypothalamic instrument receives in maintaining the internal milieu against environmental odds and mental (emotional) influences. The adrenal cortex "hormone" elevates the blood pressure, and desoxycorticosterone in large doses may produce arterial hypertension. This hormone is probably one of the agents by which hypertension of hypothalamic-pituitary origin is produced. The foregoing views are based on the statements on functional pathology by Lichtwitz (1942).

The Basis of the Treatment of Hypertension.—The unsatisfactory nature of present knowledge of the cause and treatment of hypertension is shown by the number of drugs and methods used in its control. Various surgical, dietary and pharmaceutic measures have at one time or another offered promise.

A. Sympathectomy: The chromaffin cells of the adrenal medulla have a rich nerve supply from the splanchnic nerves (sympathoadrenal system), but the effect of sympathetic denervation on the adrenal cortex is unknown.

The mechanism by which high blood pressure is lowered in man by double lumbodorsal sympathectomy (Smithwick) is not completely understood. One suggestion has been that the lowering may be due to a favorable effect on factors which combine to reduce or alter renal blood flow, which in turn results in impairment of function and in destruction of renal tissue; however, this is probably not correct as it is generally agreed that denervation of the kidneys in man and animals causes no consistent effect on the excretory function or on blood flow. Another view is that there may be an extrarenal effect such as vascular relaxation, either arterial or venous or both, or that the decrease is due in part to inhibition of or interference with adrenal secretion (White and Smithwick, 1942). The recent discovery of Victor (1945) mentioned earlier, supported by the work of Ogden and others, that partial ligation of the adrenal vessels on one side causes sustained hypertension in dogs, might provide support for this last suggestion.

Berwald and Devine (1944) stated that the rationale for sympathectomy is based on (*a*) relaxation of blood vessels of the lower limbs and the splanchnic area, (*b*) increased blood supply to the kidney and (*c*) decrease in the amount of epinephrine secreted through fear, excitement or other vasomotor stimuli.

The operation of splanchnic section denervates the adrenals as well as the kidneys, so that the adrenal denervation may be responsible for the relief (symptomatic) obtained by patients with hypertension. Vogt showed (1944), as mentioned in a previous section, that repeated injections of epinephrine in animals cause an increased output of cortical hormone and an increase in the weight of the adrenals associated with storage of lipin.

An interesting and important physiologic observation is that the patients on whom a "successful" operation was performed show similar reactions to posture and to cold after the sympathectomy, but with lower levels of blood pressure. This neurosurgical approach to the treatment of hypertension is unsatisfactory because it does not take cognizance of the primary causal factors of the disease. It merely destroys one of the several physiologic mechanisms which maintain vascular tone.

Gold (1945) expressed the belief that while sympathectomy produces impressive initial lowering of the blood pressure in hypertension the number of successful "cures" by this method will be small. He regarded the protracted inactivity and the revised attitude and habits of the patient who has subjected himself to this serious operation as the cause of the longer lasting moderate reduction of the blood pressure.

The symptomatic improvement which occurs frequently after the Smithwick operation and after thiocyanate therapy, even without lowering of the blood pressure, has still to be explained.

B. Thiocyanate Therapy: Apart from the surgical treatment for hypertension, administration of potassium thiocyanate is the only other practical method of reducing the blood pressure. The mode of action of this drug is not understood. It may act against a pressor substance. One study of interest (Healy, 1931) showed that the cut surface of the adrenal body revealed strong evidence of thiocyanate in the cortex when the potassium salt was given to rabbits, which suggests the possibility of accumulation of the drug in the adrenal glands.

C. Nonspecific or Inflammatory Reactions: Taylor and Page (1944) investigated the mechanism of the reduction of arterial pressure in hypertensive patients and animals following nonspecific and inflammatory reactions, and they showed that neither fever nor leukocytosis is the cause. They suggested that the reactions impair that function of the adrenal cortex which maintains vascular reactivity and elevated blood pressure and so produce a reduction of arterial pressure.

CONCLUSIONS

A comprehensive and critical survey of the literature dealing with arterial hypertension leads one to conclude that until further evidence becomes available it is best to regard hypertensive vascular disease as nonrenal in origin. This point of view is accepted by Ellis (1942) and by other authorities; thus, Homer Smith and others (1943) have stated that so far as the genesis of this condition is concerned the kidney appears to be the victim rather than the culprit. This is confirmed by the conclusion reached by Page (1943, 1944) that there is little evidence that persistent reduction of blood flow and oxygen utilization occurs within the kidneys except when hypertension is of long duration and severe secondary vascular change has supervened.

An attempt has been made in the present study to show that the adrenal cortex plays a major role in arterial hypertension, and much experimental and clinical data have been submitted. While there is much evidence for this point of view, final proof must still be awaited.

G. SUMMARY OF REPORTS INDICATING THE SIGNIFICANCE OF THE ADRENAL CORTEX IN ARTERIAL HYPERTENSION

The morphologic changes are given in table 1 and are described more fully in section C. The more significant experimental and clinical findings are given in the following paragraphs.

Bilateral adrenalectomy abolishes experimental renal hypertension; the hypertension can be produced if even a minute portion of the adrenal cortex is left or if the completely adrenalectomized animal is given cortical

extract (Goldblatt, 1937; Blalock and Levy, 1937; Page, 1938; Grollman, 1940; Dell'Oro, 1942).

The renin substrate hypertensinogen is a globulin formed in the liver and possibly in the adrenal cortex. It decreases and even disappears from the systemic blood of untreated adrenalectomized male dogs (Lewis and Goldblatt, 1942; Houssay and Dexter, 1942). Adequate doses of adrenal cortex hormone or of desoxycorticosterone cause a return of hypertensinogen to a normal level.

Bilateral adrenalectomy decreases the response to injections of renin (Page, 1939; Williams and others, 1939; Friedman and his associates, 1940; Remington and others, 1941; Swingle and Remington, 1944). It prevents the appearance of a substance like angiotonin in the blood when experimental hypertension is produced in the dog by injection of kaolin into the cerebral ventricles.

Adrenal cortex tissue or certain of its hormones (desoxycorticosterone or 17-hydroxy-11-dehydrocorticosterone) seem necessary for the existence

TABLE 2.—*Reports on the Production of Hypertension with Adrenocortical and Other Hormones*

Effects in man—with desoxycorticosterone:		
Cleghorn and others	1939	In Addison's disease
Ferrebee and others	1939	In Addison's disease
McGavack	1941	In Addison's disease
Perera and others	1944	In Addison's disease
Soffer and others	1940	In Addison's disease
Thorn and Firor	1940	In Addison's disease
Effects in animals—with 17-hydroxy-11-dehydrocorticosterone:		
Kuhlman and others	1939	In dogs
Remington and others	1941	In adrenalectomized dogs
Rodbard and Freed	1942	In dogs
Swingle and others	1941	In normal and adrenalectomized dogs
Briskin and others	1943	In rats
Gaudino	1945	In hypertensive adrenalectomized rats
Grollman and others	1940	In rats
Knowlton and others	1946	In rats with cytotoxic serum nephritis
Leathem and Drill	1944	In rats
Selye	1946	In rats
Effects in animals—with 17-hydroxy-11-dehydrocorticosterone:		
Guadino	1945	In hypertensive adrenalectomized rats
Effects in animals—with stilbestrol:		
Grollman and others	1940	In rats
Hill	1946	In rats
Leathem and Drill	1943	In normal and hypophysectomized rats
Oster	1946	In castrated rats
Sapeika		In rats

of "renal" hypertension and for the maintenance of normal arterial pressure.

Hypophysectomy in rats with "renal" hypertension causes a fall of blood pressure, which is restored to the original level by administration of adrenocorticotrophic hormone.

Hypophysectomy or adrenalectomy in rats with "renal" hypertension causes a fall in the level of blood pressure, which may be partially restored by the administration of adrenal cortex extracts or desoxycorticosterone but not by the use of such steroids as progesterone, testosterone or estradiol (Page and others, 1946).

Ligation of vessels to an adrenal gland produced sustained hypertension in dogs comparable with that produced by the Goldblatt method (Victor, 1945; Ogden and others, 1948).

Successful reduction of the systolic and diastolic pressures for months was obtained in cases of hypertension by subtotal bilateral adrenalectomy (DeCourcy, 1934).

In cases of Cushing's syndrome due to adrenal carcinoma the raised blood pressure returned to normal after removal of the tumor (Silver, 1940).

A patient with hypertension in whom Addison's disease subsequently developed had a persistently elevated blood pressure while receiving desoxycorticosterone (Perera, 1945).

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ORGANISMS RESISTANT TO PENICILLIN OBTAINED FROM PATIENTS

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IT IS GENERALLY supposed that bacteria which are sensitive to the action of penicillin seldom acquire resistance to this antibiotic as a result of the treatment of human infections. In most cases of infection amenable to penicillin therapy a prompt clinical response is obtained and administration is discontinued. Generally, there is little opportunity for resistant strains to develop in such cases as the period of treatment is usually of relatively short duration.

The appearance of resistant organisms while the patient was under treatment with penicillin has been reported.[1] In most of the cases the

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1. Spink, W. W.; Ferris, V., and Vivino, J. J.: Antibacterial Effect of Whole Blood upon Strains of Staphylococci Sensitive and Resistant to Penicillin, Proc. Soc. Exper. Biol. & Med. **55**:210 (April) 1944. Gallardo, E.: Sensitivity of Bacteria from Infected Wound to Penicillin: II. Results in One Hundred and Twelve Cases, War Med. **7**:100 (Feb.) 1945. North, E. A., and Christie, R.: Observations on the Sensitivity of Staphylococci to Penicillin, M. J. Australia **2**:44 (July 14) 1945. Buchman, J., and Blair, J. E.: Penicillin in the Treatment of Chronic Osteomyelitis, Arch. Surg. **51**:81 (Sept.) 1945; Report on the Use of Penicillin in the Treatment of Staphylococcal Infections, with Special Reference to Acute and Chronic Osteomyelitis and Several Collateral Studies, Bull. Hosp. Joint Dis. **6**:114 (Oct.) 1945. Todd, E. W.; Turner, G. S., and Drew, L. G. W.: "Fastness" of Staphylococci, Haemolytic Streptococci, and Pneumococci to Penicillin, Brit. M. J. **2**:603 (Nov. 3) 1945. North, E. A., and Christie, R.: Acquired Resistance of Staphylococci to the Action of Penicillin, M. J. Australia **1**:176 (Feb. 9) 1946. Blair, J. E.; Carr, M., and Buchman, J.: The Action of Penicillin on Staphylococci, J. Immunol. **52**:281 (March) 1946. Harley, H. R. S.; Baty, J. A., and Bowie, J. H.: The Pathogenicity of Penicillin-Insensitive Infection, Brit. M. J. **2**:639 (April 27) 1946. Franks, A. G.: Successful Combined Treatment of Penicillin-Resistant Gonorrhea, Am. J. M. Sc. **211**:553 (May) 1946. Mascall, W. N.: Penicillin for Gonorrhea in the Female, Lancet **2**:712 (Nov. 16) 1946. Pulaski, E. J.: Streptomycin Therapy of Penicillin-Resistant

sensitivities of the organisms had not been determined before treatment was started so that the strains may have been naturally resistant. In other cases the bacteria were isolated from open wounds and thus were exposed to contamination from outside sources, so that it is impossible to determine whether the resistant strains were derived from the organisms originally present or whether they came from the outside.

In some infections, such as staphylococcic bacteremia or endocarditis caused by Streptococcus viridans, even though recovery may take place slowly, the antibiotic usually clears the blood stream rapidly. After penicillin treatment has been started, bacteria usually cannot be obtained by culturing the blood, and consequently they are not suitable for subsequent determinations of sensitivity.

Several investigators[2] have reported the development of resistant strains of Str. viridans in patients during treatment with penicillin for endocarditis. In the course of studying 75 patients with bacteremia or endocarditis, we encountered 14 patients on whom positive blood cultures were obtained after penicillin therapy had been started. In each instance the organism was identical, so far as could be determined, with the organism present in the blood before the start of treatment. It is the purpose of the present paper to discuss the circumstances in which this phenomenon occurred and to compare the penicillin sensitivities of the organisms at various stages during the course of treatment of the disease.

Our experience with regard to the penicillin sensitivity of pneumococci and beta hebolytic streptococci has been similar to that of others. Almost all the strains tested were extremely sensitive to penicillin. In only one publication[3] has there been reported a highly resistant strain of a beta hemolytic streptococcus. We have encountered three strains of beta hemolytic streptococci and one strain of pneumococcus which were relatively resistant to penicillin. The details of these cases are being reported herewith.

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TABLE 1.—*Data on the Bacteria Developing Resistance During Penicillin Therapy*

	Patient	Diagnosis	Organism	Original Sensitivity to Penicillin (Units/Cc.)	Day of Appearance of Positive Blood Culture	Sensitivity Determination to Penicillin at Time of Relapse (Units/Cc.)	Fold Increase	Dose At Time of Change in Sensitivity (Units) *	Blood Concentrations of Penicillin (Units/Cc. Serum) 1 Hour after Injection	2 Hours after Injection	3 Hours after Injection	Result
Symptoms of Active Infection	1	Bacteremia	Staphylococcus albus, hemolytic, coagulase —	0.022	3 5 8 12	0.044 0.089 1.45 0.72	2 4 64 32	75,000 every 2 hr. orally 75,000 every 2 hr. orally 50,000 every 2 hr. None Streptomycin†	0.039	0	0	Recovered with the use of streptomycin
	2	Bacteremia	Staphylococcus aureus, hemolytic, coagulase +	0.195	7	1.45	8	100,000 every 2 hr. 500,000 every 2 hr.†	———			Infection controlled; died of debility
	3	Bacteremia	Hemolytic streptococcus	0.039	3 4	20.00 20.00	512 512	1,000,000 every 2 hr. 1,000,000 every 2 hr.† Caronamide‡	10.00	5.00	—	Recovered
	4	Endocarditis	Staph. albus, nonhemolytic, coagulase —	0.089	1 2	0.72 1.42	8 16	100,000 every 2 hr. 100,000 every 2 hr. 1,000,000 every 2 hr.†	1.25	0.312	—	Died of overwhelming infection
	5	Endocarditis; arthritis	Staph. aureus hemolytic, coagulase +	0.022	7	0.89	4	25,000 every 3 hr. 50,000 intra-articularly 50,000 every 3 hr.†	0.312 (0.625 in joint fluid)	0.156	0.039	Recovered
	6	Endocarditis	Staph. aureus, hemolytic, coagulase —	0.312§	Daily from 7 to 13	20.00	64	1,000,000 every 2 hr. 1,000,000 every 2 hr.† Caronamide‡ 2,000,000 every 2 hr.† Caronamide‡	5.00 10.00	2.5 5.00		Died of overwhelming infection
	7	Endocarditis	Staph. aureus, nonhemolytic, coagulase +	0.044	14 20 27	0.089 0.178 0.356	2 4 8	15,000 every 2 hr. 50,000 every 2 hr. 75,000 every 2 hr. 1,000,000 every 24 hr.†	0.078 0.625 1.25	0.039 0.156 0.312		Recovered
	8	Endocarditis	Staph. aureus, nonhemolytic, coagulase —	0.078	20	0.625	8	200,000 every 2 hr. 2,000,000 every 2 hr.†	———			Recovered

	Patient	Diagnosis	Organism	Original Sensitivity to Penicillin (Units/Cc.)	Day of Recurrence of Positive Blood Culture	Sensitivity of Organism to Penicillin at Time of Recurrence (Units/Cc.)	Fold Increase	Dose At Time of Change in Sensitivity (Units)*	Blood Concentrations of Penicillin (Units/Cc. Serum) 1 Hour after Injection	2 Hours after Injection	3 Hours after Injection	Result
Symptoms of Active Infection	9	Endocarditis	Str. viridans	0.0007	3 21 29 31	0.011 0.044 0.179 1.43	16 64 256 2048	100,000 every 2 hr. orally 25,000 every 2 hr. 30,000 every 2 hr. 500,000 cont. every 24 hr. 1,000,000 cont. every 24 hr.†	0.039 0.312 0.312	0 0.039 0.039 range, 0.312 to 1.25		Recovered
	10	Endocarditis	Str. viridans	0.039	8	0.625	16	30,000 every 2 hr. 60,000 every 2 hr.†	0.625	0.078		Recovered
Asymptomatic	11	Bacteremia	Staph. albus, hemolytic, coagulase —	0.089	16	0.178	2	75,000 every 2 hr.	0.625	0.312		Recovered
	12	Bacteremia	Staph. aureus, hemolytic, coagulase +	0.195	6	0.780	4	1,000,000 every 2 hr.	———			Recovered
	13	Endocarditis	Staph. aureus, hemolytic, coagulase +	0.089	2	0.178	2	75,000 every 2 hr.	0.312 0.625	0.156 0.312		Recovered
	14	Endocarditis	Str. viridans	0.019	26	0.039	2	50,000 every 3 hr.	0.625	0.312	0.156	Recovered

*All patients received penicillin intramuscularly unless otherwise indicated.
†Final dose.
‡Caronamide was given in doses of 4 Gm. every four hours.
§Recurrence of organism in blood culture during first three days of therapy without change in sensitivity.

"ACQUIRED" RESISTANCE

Of 75 patients with endocarditis and bacteremia treated with penicillin, 14 had one or more recurrences of positive blood cultures during therapy. In each instance the causative organism was found to be more resistant than at the start. Invariably, the original sensitivity was based on determinations[4] on the organism isolated from at least two different cultures taken at different times. The pertinent data from the case histories of these patients are shown in table 1. In the first 10 patients the recurrence of bacteremia was accompanied with symptoms of active infection. There were 2 patients with staphylococcic bacteremia, 1 with hemolytic streptococcic bacteremia, 5 with staphylococcic endocarditis and 2 with endocarditis caused by Str. viridans. In all but 1 of the patients bacteremia disappeared, only to recur sometime from the third to the thirty-first day of treatment with penicillin. In the patient mentioned, bacteremia persisted for the two days that penicillin was administered before his death.

The increase in resistance ranged from fourfold to two thousand and forty-eight fold. It can be seen that there is no correlation between the initial sensitivity and the height and rapidity of the development of resistance. Six strains exhibited increases on one occasion, one on two occasions, one on three occasions and two on four occasions. The blood penicillin concentrations were determined in 8 of these patients after the appearance of organisms with increased resistance which developed while the patients were still on the same dosage schedule. If one considers penicillin therapy to be adequate when the blood concentrations are always greater than the in vitro sensitivity of the organism, then there was no correlation between the development of resistance and the adequacy of therapy, since in 4 of the patients the concentrations in the blood were always bactericidal. On the other hand, if, as some investigators believe, penicillin blood concentrations four to eight times the in vitro sensitivity of the causative organisms are necessary in cases of endocarditis, none of these patients can be considered as having received adequate treatment. The dose was increased in all cases, and recovery followed in 6. One patient died of debility after the infection was controlled, 2 died of overwhelming infection and another was ultimately cured with streptomycin.

In the other group of 4 patients, 1 each with staphyloccic endocarditis and endocarditis caused by Str. viridans and 2 with staphylococcic bacteremia, the appearance of positive bacteriologic signs after treatment was begun was not accompanied with symptoms of active infection. In 1 patient bacteremia persisted through the second day of treatment, while

4. The determinations were made by the serial dilution method.

in the remaining patients bacteremia disappeared after penicillin was started, only to recur daily from the sixth to the twenty-sixth day of therapy. Three of the strains demonstrated a twofold increase in resistance and the fourth a fourfold increase. Adequate blood concentrations of penicillin were found in the 3 patients in whom they were determined. The doses of penicillin were continued and all the patients recovered.

One of the problems was to determine the significance of the increased resistance of the infective bacteria in these patients. In an occasional organism as much as an eightfold increase in sensitivity to penicillin has been observed to occur spontaneously or as a result of the inaccuracy of the method of assay. It is believed, however, that the increases in resistance to penicillin observed in the first 10 patients in table 1 represented a true change in penicillin sensitivity, since symptoms of an ac-

TABLE 2.—*Data on Bacteria Resistant to Penicillin*

Patient	Diagnosis	Organism	Source of Culture	Sensitivity (Units/Cc.)	Dose	Result
1	Scarlet fever	Hemolytic streptococcus	Throat	20	300,000 units in oil and beeswax once a day for 5 days	Recovered; penicillin ineffective
2	Pharyngitis	Hemolytic streptococcus	Throat	20	100,000 units every 4 hr. for 5 days	Recovered; penicillin ineffective
3	Erysipelas	Hemolytic streptococcus	Blood; nose; throat	>200	600,000 units in oil and beeswax for 2 doses 1,000,000 every 2 hr. for 1 dose	Died
4	Pneumonia	Pneumococcus, type I	Sputum	>20	600,000 units in oil and beeswax twice a day for 10 days	Recovered with the use of sulfadiazene

tive infection were present at the same time. On the basis of the results of the determinations of the concentrations of penicillin in the blood, it would appear that therapy given to these patients was inadequate. Furthermore, we have not noted a spontaneous change in sensitivity greater than fourfold with repeated sensitivity determinations on twenty-seven organisms transferred from two to fifty times in artificial mediums. In addition, in only one of several hundred determinations have we found a difference greater than fourfold when multiple determinations of sensitivity were performed on the same organism isolated at different times from patients not receiving specific therapy.

The significance of the increased resistance in the last 4 patients is unknown. Whether it represented a laboratory error or an actual change in sensitivity without clinical significance is a matter of speculation.

"NATURAL" RESISTANCE

Four strains of bacteria were isolated from patients before treatment was started that were apparently relatively insensitive to penicillin (table 2). Two of the strains of beta hemolytic streptococci were isolated from cultures of the throats of 2 patients with scarlet fever and septic sore throat, respectively. In neither instance was the sensitivity of the streptococcus determined before therapy was started. The patient with scarlet fever was treated with daily injections of 300,000 units of penicillin in oil and wax, and the other patient received 100,000 units of penicillin orally every four hours. After three days of therapy there was no clinical or bacteriologic improvement in either patient, and cultures of the throats revealed organisms resistant to 10 and sensitive to 20 units of penicillin per cubic centimeter of medium. Administration of penicillin was continued for two additional days, and the course was that usually seen in patients treated symptomatically.

The third patient was admitted to the hospital with symptoms and signs of acute sinusitis and pneumonia. After cultures of material from the throat and blood cultures were taken, she was placed on a regimen of 600,000 units of penicillin in oil and wax every twelve hours. The following day erysipelas of the face developed. In the meantime, a beta hemolytic streptococcus was isolated from the throat and blood cultures. Both strains were found to be resistant to 20 units of penicillin per cubic centimeter of medium. Within the period that it took to determine the sensitivities the patient died. At autopsy there were no abnormalities except for the erysipelas and evidence of toxic changes in the various organs incident to the infection.

The fourth patient was admitted to the hospital with symptoms and signs of pneumonia of the upper lobe of the right lung. A type I pneumococcus was isolated from his sputum. After two days of therapy consisting of 600,000 units of penicillin in oil and wax every twelve hours, during which time there was no improvement, the sensitivity of the organism was determined, and it was found to be resistant to 200 units of penicillin per cubic centimeter of medium. The patient's condition was later diagnosed as pulmonary tuberculosis, so that the significance of the pneumococcus is undetermined. In any event, the epidemiologic significance of this strain is obvious.

COMMENT

Three theories of the development of resistance have been proposed: adaptation, mutation and selection.[5] The first two theories suppose that

5. Demerec, M.: Production of Staphylococcus Strains Resistant to Various Concentrations of Penicillin, Proc. Nat. Acad. Sc. 31:161 (Jan.) 1945.

all members of the bacterial population were originally sensitive and that as a result of exposure to penicillin there occurs some change in their physical-chemical state or in their metabolic requirements. The third theory proposes that in any bacterial population the sensitivity of the members varies and that resistant members or mutants are present originally. On exposure to penicillin the sensitive members are killed, while the resistant members survive (survival of the fittest). The resistant members apparently may not influence the original determination of sensitivity because of their limited numbers. Under the conditions of the test, the organisms do not proliferate sufficiently to influence the result.

Regardless of the mechanism involved, subbactericidal concentrations of penicillin apparently are a prerequisite for the development of resistance. Inadequate penicillin therapy may be the result of insufficient amounts of the antibiotic or of unusually rapid excretion by the patient. In certain infections such as endocarditis and osteomyelitis, in which, because of the nature of the lesions or the avascularity of the tissue, the penetration of penicillin into the tissues is poor, there is greater opportunity for resistance to develop. Furthermore, certain bacteria such as staphylococci and Str. viridans develop resistance with great facility. In the 10 patients in whom the causative organism developed increased resistance to penicillin one or more of these factors were probably operative.

It is obvious from the data in table 1 that the initial sensitivity to penicillin is not a factor in the development of the resistance, although it has been suggested that strains relatively insensitive originally develop resistance with greater ease. The data indicate that there was great variation in the speed and height of the development of resistance, but we were unable to determine any factors which governed this phenomenon.

As a result of these and other studies, we have found that the penicillin sensitivity may serve as an aid in the identification of bacteria. We have noted many instances in which organisms isolated at different times were alike in all their cultural characteristics except the penicillin sensitivity, and ultimately it was concluded that actually there were different strains.

Penicillin-sensitive bacteria have developed resistance in the test tube on exposure to increasing sublethal concentrations of penicillin and during the treatment of infections in human beings with inadequate doses. In addition, naturally resistant strains have been observed among the bacteria generally susceptible to penicillin. These laboratory and clinical observations confirm the necessity for adequate bacteriologic study and follow-up on all patients receiving antibiotic therapy whenever possible. In cases of endocarditis and infections caused by staphylococci and certain strains of Str. viridans the sensitivity to penicillin should be determined and treatment arranged accordingly. Furthermore, in order to

insure adequate concentrations in the tissues and also to compensate for errors in the method of determination of sensitivity, blood penicillin concentrations four to eight times the in vitro sensitivity should be maintained. These precautions will help to minimize the development of resistant organisms during therapy with penicillin.

SUMMARY AND CONCLUSIONS

1. Fourteen of 75 patients with infections of the blood stream had a recurrence of positive blood cultures during penicillin therapy. All the organisms demonstrated an increase in resistance to penicillin. In 10 patients the increase in resistance was fourfold or greater and was accompanied with symptoms of active infection. The increased resistance of the organisms in 4 patients was fourfold or less and not accompanied with symptoms of infection.

2. Three strains of beta hemolytic streptococci and one strain of a type I pneumococcus were isolated which were resistant to penicillin before therapy was begun.

3. In cases of bacteremic or other serious infections caused by staphylococci or alpha and gamma streptococci the sensitivity of the organism to penicillin should be determined before treatment is instituted and careful bacteriologic follow-up should be maintained.

4. In cases of infections which are usually amenable to penicillin therapy the sensitivity of the causative organism should be determined when there is no response to treatment.

Book Review

Sexual Behavior in the Human Male. By Alfred C. Kinsey, Wardell B. Pomeroy and Clyde E. Martin. Price, $6.50. Pp. 804, Philadelphia: W. B. Saunders Company, 1948.

This study is a monumental contribution to our knowledge of the sexual behavior of the human male. It is accurately described by its authors as "a fact-finding survey . . . to discover what people do sexually, and what factors account for differences in sexual behavior among individuals, and among various segments of the population." The data have all been obtained in personal interviews, each of approximately two hours' duration. To date, 12,000 persons have been studied; of these, 6,300 are males and 5,300 white males on which the present volume is based. The conclusions are of far reaching import and deserve the attention not only of medical men but of all of those who are seriously interested in our American social scene.

Certain criticisms, for the most part pointed out frankly by the authors, are legitimate but scarcely detract from the value of the work. For example, it is a study not of all kinds of men but only of white men in the United States and in the twentieth century. It is, furthermore, rather heavily weighted with an urban and academic selection; it samples too few men over 50 years of age, too few factory workers and manual laborers and too few children, and it reserves for future reports all consideration of the highly interesting Negro male. Further, it is, of course, a study only of what men *say* they do. Despite scrupulous and ingenious cross checks and guards against falsification, it is necessarily colored somewhat by the errors of memory, by the fact that some men are given to boasting and others to reticence and by unconscious tendencies in the individual to say about himself what he considers to be "normal" or expected. Unfortunately, no study of large numbers can in any sense measure the subtle psychologic factors underlying sexual behavior or the emotional tones accompanying it. Finally, as others have pointed out, this report is a record of the testimony only of those men who chose to testify and misses those who for one reason or another refused.

With all these reservations, it must be admitted that the work is in general a fair documentation of the sexual life of the modern white American male. The interview method, with all its limitations, is indisputably far superior to the almost worthless questionnaire method. And for extensive coverage, wealth of detail and meticulous and critical statistical analysis, the study is incomparable in medical and sociologic literature.

To medical readers, and especially to psychiatrists, many of the revelations in the book come as no surprise. For example, physicians have long known or suspected the early development of erotic interests and overt sexual behavior and the high incidence of masturbation (92 per cent among the male population), of isolated (but not habitual) homosexual experiences (37 per cent) and of premarital (67 to 98 per cent) and extramarital (about 50 per cent) heterosexual

indulgence. However, it is arresting to learn of the differences in sexual behavior between the lower and higher educational and social strata and the rather widely divergent customs and taboos in the two groups. These differences are so great that it is no longer legitimate to speak of the sexual habits of the average man without specifying which average is meant. Of great interest also is the doubt, expressed by the authors in a long and closely reasoned passage, as to the existence of the commonly accepted idea of "sublimation."

In a review of this sort no extended critique can be given. But for every serious physician this landmark in sociologic fact finding is not only an indispensable source of information on a topic too long left to conjecture but also an absorbingly interesting one.

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